March 11, 2022
Medical Device Evaluation Division
Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Report on the Deliberation Results

Classification	1. Instrument & Apparatus 51, Suckers, Tubes and Catheters for Infusion or Drainage 2. Instrument & Apparatus 29, Electrosurgical Unit
Term Name	1. Atherectomy ablative angioplasty catheter 2. Driving unit for atherectomy angioplasty catheter
Brand Name	1. C^2 Coronary IVL Catheter 2. IVL Generator
Applicant	Shockwave Medical, Inc.
Designated Marketing Authorization Holder	Vorpal Technologies K.K.
Date of Application	March 26, 2021 (Application for marketing approval of a medical device manufactured in a foreign country)

Results of Deliberation

In its meeting held on March 11, 2022, the Committee on Medical Devices and *In-vitro* Diagnostics reached the following conclusion, and decided that this conclusion should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product should be approved with no designation as a medical device subject to a use-results survey. The product is not classified as a biological product or a specified biological product.

Review Report

February 15, 2022
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following medical device submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Classification	1. Instrument & Apparatus 51, Suckers, Tubes and Catheters for Infusion or Drainage 2. Instrument & Apparatus 29, Electrosurgical Unit
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Reviewing Office	Office of Medical Devices I

Review Results

February 15, 2022

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Results of Review

The C^2 Coronary Intravascular Lithotripsy (IVL) Catheter (hereinafter referred to as the IVL Catheter) is intended to be used to disrupt calcified, *de novo* coronary lesions, which is used together with the IVL Generator. The IVL Catheter contains 2 emitter stations with 2 integrated lithotripsy emitters for the delivery of acoustic pressure pulses in the balloon. Electrical energy in the form of direct-current pulses delivered from the IVL Generator to the lithotripsy emitters is converted to acoustic pressure pulses, which are delivered to the target lesion through the balloon to disrupt the calcified lesion (the combination of the IVL Catheter and the IVL Generator is hereinafter referred to as the IVL System).

The applicant submitted non-clinical data supporting the electric safety and electromagnetic compatibility, biological safety, stability and durability, performance, directions for use, and software development life cycle process. There was no particular problem in the submitted data.

The applicant submitted the results of the following clinical studies: “Disrupt CAD III Study,” a clinical study in the United States (US) and Europe, and “Disrupt CAD IV Study,” a clinical study in Japan.

The Disrupt CAD III Study was a multicenter, prospective, single-arm study to evaluate the efficacy and safety of the IVL System for the treatment of severely calcified, *de novo* coronary lesions prior to stenting. The primary safety endpoint of “major adverse cardiovascular event (MACE)-free rate at 30 days (30-day MACE-free rate)” was 92.2% (353 of 383 subjects, the lower bound of the one-sided 95% confidence interval of 89.9%), which was higher than the pre-specified performance goal of 84.4%. The primary efficacy endpoint of the “rate of procedural success defined as stent delivery with

a residual in-stent stenosis <50% (core laboratory assessed) and without in-hospital MACE" was 92.4% (355 of 384 subjects, the lower bound of the one-sided 95% confidence interval of 90.2%), which was higher than the pre-specified performance goal of 83.4%.

The Disrupt CAD IV Study was a multicenter, prospective, single arm study in Japanese subjects enrolled using similar eligibility criteria to those of the Disrupt CAD III Study. The Japanese study was intended to verify the extrapolation of data from the Disrupt CAD III Study to the Japanese population. The primary safety endpoint of "30-day MACE-free rate" was 93.8% (60 of 64 subjects), which was not inferior to that in the matched cohort of the Disrupt CAD III Study (91.2%, 291 of 319 subjects). The primary efficacy endpoint of the "rate of procedural success defined as stent delivery with a residual in-stent stenosis <50% (core laboratory assessed) and without in-hospital MACE" was 93.8% (60 of 64 subjects), which was not inferior to that in the matched cohort of the Disrupt CAD III Study (91.6%, 293 of 320 subjects).

On the basis of the comprehensive review of the submitted data in light of comments from the Expert Discussion, PMDA concluded that the IVL System is an effective and safe medical device that supports the dilatation of severely calcified, *de novo* coronary lesions.

As a result of its review, PMDA has concluded that the IVL System may be approved for the following intended use and that the results should be presented to the Committee on Medical Devices and *In-vitro* Diagnostics for further deliberation.

Intended Use of the IVL Catheter

C^2 Coronary IVL Catheter is intended to be used to disrupt severely calcified, *de novo* coronary lesions, allowing subsequent dilatation of a coronary artery stenosis.

Intended Use of the IVL Generator

IVL Generator is intended to be used to disrupt severely calcified, *de novo* coronary lesions.

Review Report

February 15, 2022

Product for Review

Classification	1. Instrument & Apparatus 51, Suckers, Tubes and Catheters for Infusion or Drainage 2. Instrument & Apparatus 29, Electrosurgical Unit
Term Name	1. Atherectomy ablative angioplasty catheter 2. Driving unit for atherectomy angioplasty catheter
Brand Name	1. C^2 Coronary IVL Catheter 2. IVL Generator
Applicant	Shockwave Medical, Inc.
Designated Marketing Authorization Holder	Vorpal Technologies K.K.
Date of Application	March 26, 2021 (Application for marketing approval of a medical device manufactured in a foreign country)
Proposed Intended Use	1. C^2 Coronary IVL Catheter is intended to be used in intravascular lithotripsy for calcified, *de novo* coronary lesions. 2. IVL Generator is intended to be used in intravascular lithotripsy for calcified, *de novo* coronary lesions.

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List of Abbreviations

ASTM	American Society for Testing and Materials
CABG	Coronary Artery Bypass Graft
CEC	Clinical Events Committee
CK-MB	Creatine Kinase MB
CRT-D	Cardiac Resynchronization Therapy with Defibrillator
CVIT	Japanese Association of Cardiovascular Intervention and Therapeutics
DCB	Drug Coated Balloon
DES	Drug Eluting Stent
IABP	Intra-Aortic Balloon Pump
ICD	Implantable Cardioverter Defibrillator
IDE	Investigational Device Exemption
IEC	International Electrotechnical Commission
ISO	International Organization for Standardization
ITT	Intent to Treat
IVL	Intravascular Lithotripsy
IVUS	Intravascular Ultrasound
MACE	Major Adverse Cardiovascular Events
MI	Myocardial Infarction
OCT	Optical Coherence Tomograph
PCI	Percutaneous Coronary Intervention
POBA	Percutaneous Old Balloon Angioplasty
PTCA	Percutaneous Transluminal Coronary Angioplasty
SD	Standard Deviation
STEMI	ST-Elevation Myocardial Infarction
TLR	Target Lesion Revascularization
TVR	Target Vessel Revascularization

I. Product Overview

The C^2 Coronary Intravascular Lithotripsy (IVL) Catheter (hereinafter referred to as the IVL Catheter) is a rapid-exchange coronary balloon catheter. The IVL Catheter contains 2 emitter stations with 2 integrated lithotripsy emitters for the delivery of acoustic pressure pulses in the balloon. The IVL Catheter is used with a 0.014-inch guidewire and is inserted through a 6 Fr guiding catheter to a target lesion. The balloon length of the IVL Catheter is 12 mm. The IVL Catheter is available in 4 sizes according to the balloon diameter (2.5, 3.0, 3.5, and 4.0 mm in diameter).

The IVL Generator consists of an IVL generator, an IVL connector cable, and accessories (Charger Module, AC Mains Cable, and mounting bracket). The IVL Generator is used together with the IVL Catheter (hereinafter the combination of the IVL Catheter and the IVL Generator referred to as the IVL System) (Figure 1). The IVL Generator automatically identifies the model information of the IVL Catheter in use and delivers electrical pulses to the IVL Catheter through button operation with the IVL Connector Cable. The IVL Generator delivers 10 pulses for the time of 10 seconds while the button on the IVL Connector Cable is kept pressed. The IVL Generator is programmed to force a minimum pause time of 10 seconds following every 10 pulses delivered. The pre-programmed maximum total number of pulses per catheter is 80.

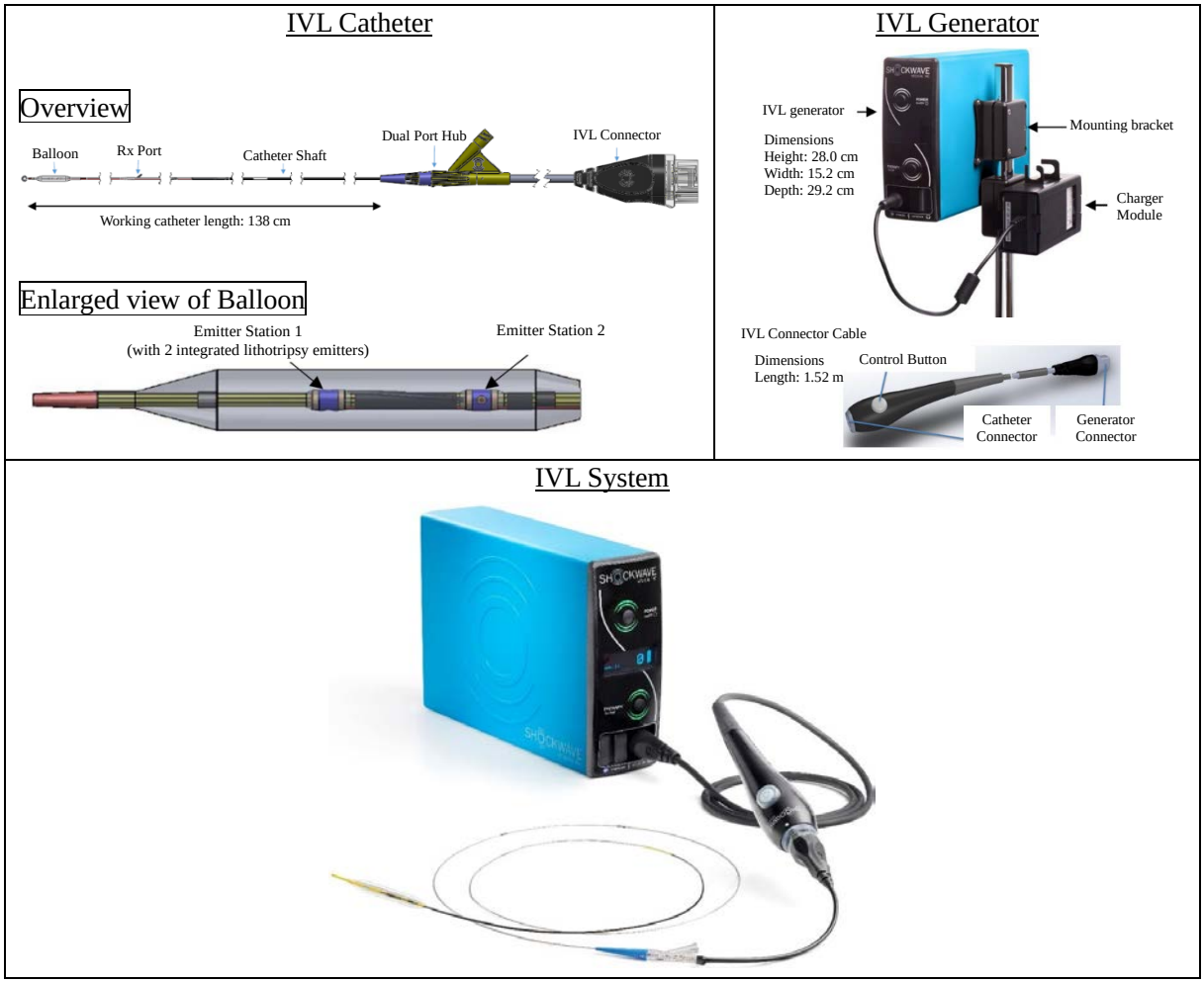

Figure 1. External view of the IVL System

The IVL System utilizes the lithotripsy technology, which disrupts calcium with pulses, and the balloon technology. The IVL System is designed to dilate the target blood vessel by disrupting the calcified lesion prior to PCI. In this technique, the balloon is inflated at a lower pressure than the nominal balloon pressure after the IVL Catheter is placed within the target lesion. Electrical energy in the form of direct-current pulses, delivered from the IVL Generator to the lithotripsy emitters, is converted to acoustic pressure pulses, which are delivered to the target lesion through the balloon to disrupt the calcified lesion (Figure 2). Following the delivery of acoustic pressure pulses, the balloon is inflated according to the balloon compliance chart, while monitoring the lesion status under fluoroscopy. Additional acoustic pressure pulse treatment can be performed, if deemed necessary, until the lesion has been sufficiently dilated (this pulsing sequence with the IVL System is referred to as Intravascular Lithotripsy [IVL]). The users must take care not to exceed 80 pulses maximum in the same treatment segment and therefore 160 pulses maximum in an overlap segment when multiple inflations are required due to a lesion length greater than the balloon length.

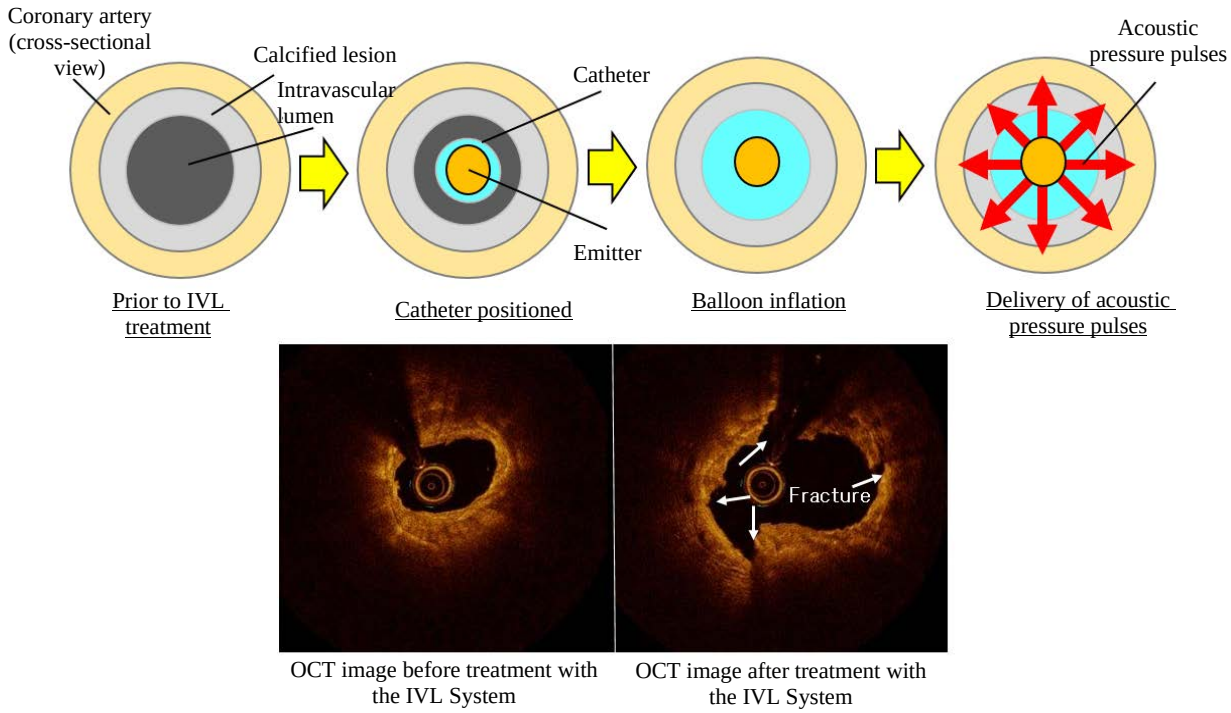

Figure 2. Disruption process of calcified lesion with the IVL System

II. Summary of the Data Submitted and Outline of the Review Conducted by the Pharmaceuticals and Medical Devices Agency

The data submitted in support of the present application by the applicant and the applicant's responses to the inquiries from the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined below.

The expert advisors present during the Expert Discussion on the IVL System declared that they did not fall under Item 5 of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1. History of Development, Use in Foreign Countries, and Other Information

1.A Summary of the data submitted

1.A.(1) History of development

Coronary artery calcification is especially common in the elderly and patients with advanced arterial sclerosis. The current standard percutaneous coronary intervention (PCI) to treat coronary artery calcification are atherectomy, balloon angioplasty, and stenting. Calcified lesions are, however, reportedly associated with an increased risk of target lesion revascularization (TLR) because of dilatation failure, balloon rupture, vascular dissection, stent delivery failure, or restenosis. This is one of the remaining challenges with PCI.[1,2,3]

Several mechanisms are thought to be involved in the poor outcomes of patients with coronary calcification after PCI. Severely calcified lesions are often associated with incomplete or asymmetric stent expansion, which increases the risks of restenosis or stent thrombosis.[2] Correction of incomplete stent expansion with a high-pressure balloon may lead to coronary artery rupture or dissection.[1,2] Furthermore, difficulties in stent delivery may result in structural damage to the device. In particular, a troublesome delivery of a drug-eluting stent (DES) may cause the polymer/drug coating to peel off to interrupt the drug delivery, which may cause restenosis or stent thrombosis.[3]

Prior to PCI, coronary artery calcification is treated by dilatation with a high-pressure balloon catheter, a cutting balloon (a special balloon with blades), or atherectomy devices such as “Rotablator” (Approval No. 20900BZY00356000) and “Diamondback 360 Coronary Orbital Atherectomy System” (Approval No. 22900BZI00004000). However, the pretreatment of the severely calcified coronary artery with these techniques is associated with specific risks, i.e., vascular dissection with high-pressure balloon dilatation and vascular perforation with dilatation with the cutting balloons. In addition, the efficacy of the techniques for lesion dilatation is limited. Atherectomy devices can cut off calcified lesions to open the vascular lumen. It is, however, not easy to control the site and amount for cutting. Excessive removal of the vascular tissue is associated with the risks of vascular perforation, peripheral embolism, and aneurysm.

To address these challenges, the applicant has developed the IVL System using lithotripsy and balloon technologies. The IVL System may reduce the risks of complications, such as vascular dissection, vascular perforation, acute coronary occlusion, slow flow, and no reflow, because it does not cut calcified lesions but dilates the coronary artery using a lower pressure balloon (4-10 atm) than the conventional high-pressure balloon (20 atm at maximum). In addition, the IVL System delivers acoustic pressure pulses towards all directions around the blood vessel, which is expected to provide a therapeutic effect, regardless of the eccentricity of the lesion.

The first-generation IVL Catheter and the IVL Generator were developed and the first-in-human trial was conducted. After that, the Disrupt CAD I Study was conducted using this system in Europe and Australia to evaluate the safety and performance of this system in the pretreatment of calcified, *de novo* coronary lesions for successful stenting. On the basis of the data from this study, the system was granted CE mark clearance in April 2017. In Europe, the Disrupt CAD II Study was conducted as a post-marketing study.

Subsequently, the second-generation IVL Catheter was developed to improve the passability, flexibility, operability, and kink resistance. Using the second-generation IVL Catheter, the Disrupt CAD III Study, designed as an Investigational Device Exemption (IDE) study, was planned in the US, for which patient enrollment was started in January 2019. The Disrupt CAD IV Study was planned in Japan to extrapolate the data from the Disrupt CAD III Study to the Japanese population. Patient enrollment for this study was started in November 2019. While the Disrupt CAD III Study was being conducted, the second-generation IVL Catheter was modified by slightly increasing the balloon double wall thickness (the IVL Catheter proposed in the present application) to improve the structural stability of the balloon and reduce the potential for loss of pressure during treatment. The Japanese Disrupt CAD IV Study used only the IVL Catheter. The results of the Disrupt CAD III and Disrupt CAD IV Studies are the grounds for the present application.

1.A.(2) Use in foreign countries

Table 1 shows the information regarding the approval status and sales performance of the IVL System in foreign countries.

Table 1. Approval status in foreign countries (as of December 7, 2021)

Country	Brand name	Date of approval	Intended use or indication	Numbers of devices sold
US	Shockwave C^2 Coronary Intravascular Lithotripsy (IVL) System with Shockwave C^2 Coronary IVL Catheter	February 2021 (P200039)	The Shockwave IVL System with the Shockwave C^2 Coronary IVL Catheter is indicated for lithotripsy-enabled, low-pressure balloon dilatation of severely calcified, stenotic *de novo* coronary arteries prior to stenting.	Catheter: [redacted] Generator: [redacted]
Europe	Shockwave C^2 Coronary Intravascular Lithotripsy Catheter	June 2018	The Shockwave C^2 Coronary IVL System is indicated for lithotripsy-enhanced, low-pressure balloon dilatation of calcified, stenotic *de novo* coronary arteries prior to stenting.	Catheter: [redacted] Generator: [redacted]

[redacted] catheters and [redacted] generators were sold in a total of 31 countries, including Brazil, Israel, and Australia, other than the above country and region.

1.A.(3) Malfunctions and adverse events reported in foreign countries

Tables 2 to 4 show common device malfunctions and adverse events (incidence ≥0.01%) reported for the IVL System in foreign countries as of December 7, 2021.

Table 2. Common malfunctions reported in foreign countries (IVL Catheter)

Malfunctions	Number of malfunctions	Incidence (%)
Balloon rupture/loss of pressure	[redacted]	1.31
Catheter error displayed on the IVL Generator (failure to detect the new catheter, failure to identify the IVL System, failure of the generator to supply pulse energy to the IVL System within a pre-set time limit)	[redacted]	0.32
Shaft kink or damage/hub damage	[redacted]	0.11
Failure to display the catheter connected to the generator on its screen	[redacted]	0.06
Poor passage at lesion site	[redacted]	0.06
Catheter shelf life (the past use of the IVL System detected, intermittent connection to the printed-circuit board)	[redacted]	0.04
Electric short/irregular pulses at the hub	[redacted]	0.04
Failure to reach the lesion	[redacted]	0.04
Poor connection	[redacted]	0.02
Shaft damage	[redacted]	0.02
Dissection	[redacted]	0.02
Malfunctions unrelated to the manufacturer (uncleanliness because a doctor or other user dropped the IVL System, damage to the IVL System during shipping)	[redacted]	0.01
Death	[redacted]	0.01
Perforation	[redacted]	0.01
Pacing	[redacted]	0.01
Others	[redacted]	0.07

Table 3. Common malfunctions reported in foreign countries (IVL Generator)

Malfunctions	Number of malfunctions	Incidence (%)
Error display regarding electricity supply stability (error to be displayed when internal voltage is beyond the acceptable range)	[redacted]	0.21
Problems regarding the power source of the generator (failure to maintain charging, failure to turn on the power of the IVL System)	[redacted]	0.13
Air bubbles in the front panel	[redacted]	0.06
Battery charge failure	[redacted]	0.05
System error	[redacted]	0.02
Non-product-related problem (complaint related to dropping of the IVL System)	[redacted]	0.01
Complaint about the failure to detect product problems	[redacted]	0.01
System connection	[redacted]	0.01
Damage to the IVL Generator because of dropping	[redacted]	0.01
Pulse output failure	[redacted]	0.01
Damage to the outer box	[redacted]	0.01
Others	[redacted]	0.04

Table 4. Common malfunctions reported in foreign countries (IVL Connector Cable)

Malfunctions	Number of malfunctions	Incidence (%)
Connector cable failure/complaint about poor connection to the system (complaint about the failure to detect product problems)	[redacted]	0.04
The IVL Generator detected an error and stopped operating (this problem solved by changing the connector cable)	[redacted]	0.01
Connection cut	[redacted]	0.01

1.B Outline of the review conducted by PMDA

PMDA asked the applicant to explain the relatively high incidence of balloon rupture/loss of pressure among other malfunctions reported in foreign countries.

The applicant's explanation:

Balloon rupture/loss of pressure is expected to occur during the treatment with the IVL System at a certain frequency because the IVL System is used to treat calcified lesions and calcification is associated with an increased risk of balloon rupture in PCI. As part of continuous improvement efforts

in product development, the second-generation IVL Catheter was modified during the period of the Disrupt CAD III Study by slightly increasing the balloon double wall thickness to improve the structural stability of the balloon and reduce the potential for loss of pressure during treatment. This modification decreased the incidence of balloon rupture/loss of pressure, as confirmed by an analysis of the results from the Disrupt CAD III Study. The risk of balloon rupture/loss of pressure appears to cause no particular problems. There has been no recall or other measures related to malfunctions of the IVL System overseas.

PMDA views:
The IVL System is associated with a certain level of risk of balloon rupture/loss of pressure because it is used to treat calcified lesions. To reduce the risk, an appropriate risk mitigation measure has been taken. On the basis of the clinical data and risk mitigation measures described later in Section 6, this risk was clinically acceptable and not particularly problematic.

2. Design and Development

2.(1) Performance and safety specifications

2.(1).A Summary of the data submitted

The proposed performance specifications for the IVL Catheter consist of nominal balloon diameter at recommended pressure, balloon working length at recommended pressure, balloon deflation time, kink resistance, maximum tensile strength, leakage, catheter system burst test, maximum balloon inflation pressure, balloon durability, acoustic pressure pulse output, maximum total number of pulses, surface, radiopacity, corrosion resistance, hub compatibility, particulate matters, and coating performance. The proposed safety specifications for the IVL Catheter consist of biological safety and bacterial endotoxins.

The proposed performance specifications for the IVL Generator consist of output waveform, pulse frequency, output voltage, and output electrical current. The proposed safety specifications for the IVL Generator consist of electrical safety and electromagnetic compatibility.

2.(1).B Outline of the review conducted by PMDA

For the performance specifications for the IVL System regarding the disruption of calcified lesions, including acoustic pressure pulse output, PMDA asked the applicant to explain how to evaluate the concept of disruption of calcified lesions by the IVL System, to verify the product design, and to establish the specifications in the development process.

The applicant's explanation:
An optical coherence tomograph (OCT) sub-study of the Disrupt CAD I Study showed dilated lumens with calcium fractures in calcified lesions, which resulted in increased vessel compliance during subsequent stenting and more calcium fractures with dilated lumens in the acute phase. [redacted]. Design verification tests were conducted to establish the specifications for output waveform, pulse frequency, output voltage, and output electrical current of the IVL Generator. In

addition, a test on acoustic pressure pulse output was conducted to verify acoustic pressure pulse energies generated by the lithotripsy emitters of the IVL System to establish the specifications.

PMDA accepted the applicant's explanations on the development process, design verification, and specifications of the IVL System. PMDA reviewed the data supporting the proposed performance and safety specifications to evaluate the appropriateness of the tests and specification limits, and concluded that there was no particular problem in the submitted data.

2.(2) Physicochemical properties

2.(2).A Summary of the data submitted

The applicant omitted the data on the physicochemical properties of the IVL System because they are included in the data for review in Section "2.(6) Performance" described later.

2.(3) Electrical safety and electromagnetic compatibility

2.(3).A Summary of the data submitted

To support the electrical safety and electromagnetic compatibility of the IVL System, the applicant submitted data indicating that the IVL System conforms to the standards that specify the general requirements for basic safety and essential performance of medical electrical equipment (International Electrotechnical Commission [IEC] 60601-1:2005/AMD1:2012) and the standards that specify the electromagnetic compatibility of medical electrical equipment (IEC 60601-1-2:2014).

2.(3).B Outline of the review conducted by PMDA

PMDA reviewed the data supporting the electrical safety and electromagnetic compatibility of the IVL System, and concluded that there was no particular problem in the submitted data.

2.(4) Biological safety

2.(4).A Summary of the data submitted

To support the biological safety of the IVL Catheter, the applicant submitted the results of biological safety studies of the IVL Catheter conducted in accordance with the "Basic principles of biological safety evaluation required for marketing application for medical devices (in Japanese)" (PFSB/ELD/OMDE Notification No. 0301-20, dated March 1, 2012) and the International Organization for Standardization (ISO) 10993-1. The IVL Catheter was subjected to tests for cytotoxicity, sensitization, intracutaneous reactivity, acute systemic toxicity, material-mediated pyrogenicity, hemocompatibility (American Society for Testing and Materials [ASTM] standards for hemolysis, complement activity, and thrombogenicity tests), and chemical properties. The results of these tests showed no problem.

This section is not applicable to the IVL Generator because it does not come into contact with the body.

2.(4).B Outline of the review conducted by PMDA

PMDA reviewed the data supporting the biological safety of the IVL Catheter, and concluded that there was no particular problem in the submitted data.

2.(5) Stability and durability

2.(5).A Summary of the data submitted

Since all of the raw materials of the IVL Catheter are commonly used in disposable medical devices, the applicant omitted the submission of test results supporting the stability of the IVL Catheter and submitted a self-declaration stating that its shelf life was determined based on the results of necessary stability studies in accordance with the "Handling of stability studies related to the determination of the shelf life in the application for marketing approvals (certifications) of medical devices (in Japanese)" (PFSB/ELD/OMDE Notification No. 1227-5, dated December 27, 2012). Material deterioration due to radiation sterilization was tested using appropriate samples taking into consideration the maximum possible dose estimated from the sterilization dose distribution. The test verified the performance of the IVL Catheter. On the basis of this result, the applicant omitted the submission of data on material deterioration and submitted a self-declaration stating the assurance of performance of the radiation-sterilized IVL Catheter in accordance with the "Partial Revision of 'Points to Consider in Preparing Summary Technical Documentation (STED) for Medical Devices'" (PSEHB/MDED Notification No. 0228-7, dated February 28, 2018).

The applicant omitted the submission of data supporting the stability and durability of the IVL Generator because it requires no particular storage condition and does not lose its quality over time.

The shelf life of 2 years has been proposed for the IVL Catheter. The IVL Generator has no proposed shelf life.

2.(5).B Outline of the review conducted by PMDA

PMDA reviewed the data supporting the stability and durability of the IVL Catheter, and concluded that there was no particular problem in the submitted data.

2.(6) Performance

2.(6).A Summary of the data submitted

To support the performance of the IVL Catheter, the applicant submitted the results of tests for guidewire compatibility, guiding catheter compatibility, nominal balloon diameter at recommended pressure, balloon compliance, balloon working length at recommended pressure, balloon deflation time, distal tip, position of the radiopaque marker, working length, kink resistance, maximum tensile strength, emitters and marker band integrity, leakage, catheter system burst test, maximum balloon inflation pressure, balloon durability, temperature rise, acoustic pressure pulse output, maximum total number of pulses, surface, radiopacity, corrosion resistance, hub compatibility, and particulate matters. The results of all of the tests met the predefined acceptance criteria.

To support the performance of the IVL Generator, the applicant submitted the results of tests for output waveform, pulse frequency, output voltage, output electrical current, and system conformance. The results of all of the tests met the predefined acceptance criteria.

2.(6).B Outline of the review conducted by PMDA

PMDA reviewed the data supporting the performance of the IVL System, and concluded that there was no particular problem in the submitted data.

2.(7) Directions for use

2.(7).A Summary of the data submitted

To support the directions for use of the IVL System, the applicant submitted the results of a sham study in pigs to evaluate effects at [redacted] after treatment with the IVL System.

In this study, pig coronary arteries subjected to stenting after the treatment of [redacted] with the IVL System (IVL group) were compared with those subjected to stenting after balloon angioplasty (control group). The pulse frequency was determined based on the maximum total number of pulses in humans. Angiography at [redacted] post-procedure was performed to assess clinical success, which was defined as [redacted].

[redacted] pigs were used in the study, and [redacted] main coronary arteries (left anterior descending artery, left circumflex artery, and right coronary artery) were treated with the IVL System or balloon for dilatation. Table 5 shows treatment assignments in the study. After each treatment, a bare metal stent was placed in each blood vessel. The vascular diameter and condition were determined using intravascular ultrasound (IVUS) before and after the procedure. Subsequently, the pigs were euthanized at [redacted] post-procedure for necropsy and histopathology.

Table 5. Treatment assignments in the animal study

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

No complication occurred during treatment [redacted]. There was no thrombogenicity in either the IVL group or the control group. Post-procedure angiography confirmed a satisfactory blood flow in all of the blood vessels tested, with no evidence of distal embolism. [redacted]

Histopathology showed no gross abnormalities in the necropsied coronary arteries. X-ray confirmed that all of the stents and struts were in good condition and expanded homogenously at the expected position relative to the arterial wall. Histology revealed moderate or severe granulomatous inflammation in [redacted] of [redacted] stents ([redacted] for the IVL group, [redacted] for the control group). In the study of [redacted], however, granuloma equally occurred in both the IVL and control groups. These findings suggested that the granulomatous inflammation was caused by the bare metal stents.

The final angiology at [redacted] confirmed success, which was defined as [redacted], in both the IVL and control groups.

2.(7).B Outline of the review conducted by PMDA

PMDA's view:

The study results indicate no particular problems with the safety of the IVL System for use in the normal blood vessels. However, given that a calcified lesion model cannot be created due to the limitations of the animal model, the efficacy and safety of the IVL System for the treatment of calcified coronary arteries should be evaluated using clinical study results described later, together with the animal study data.

PMDA reviewed the data supporting the directions for use of the IVL System, and concluded that there was no particular problem in the submitted data.

2.(8) Conformity to IEC 62304

2.(8).A Summary of the data submitted

The applicant submitted data demonstrating that the IVL System meets the international standards (IEC 62304: 2006/AMD1 2015) that specify the software life cycle processes of medical device software.

2.(8).B Outline of the review conducted by PMDA

PMDA reviewed the data supporting the conformity of the IVL System to IEC 62304, and concluded that there was no particular problem in the submitted data.

3. Conformity to the Requirements Specified in Paragraph 3 of Article 41 of Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices

3.A Summary of the data submitted

The applicant submitted a declaration of conformity declaring that IVL System meets the standards for medical devices as stipulated by the Minister of Health, Labour and Welfare in accordance with Paragraph 3 of Article 41 of Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (hereinafter referred to as "the Essential Principles") (MHLW Public Notice No. 122, 2005).

3.B Outline of the review conducted by PMDA

PMDA reviewed the conformity of the IVL System to the Essential Principles as shown below.

(1) PMDA's view on the conformity of the IVL System to Article 1, which defines preconditions, etc. for designing medical devices, (particularly, user conditions, such as technical knowledge and experience of intended users and education and training for intended users):

As described later in Section "6.B Outline of the review conducted by PMDA," the IVL System utilizes the conventional balloon catheter technology for PCI. Clinical study results suggest that learning curves are almost flat. On the other hand, the IVL System and the conventional medical devices have different therapeutic principles for PCI. Precautionary information based on the principle and characteristics of the IVL System, as well as training programs, including the identification of eligible patients, should be provided to users.

(2) PMDA's view on the conformity of the IVL System to Article 3, which specifies requirements for the performance and functions of medical devices, and to Article 6, which specifies the efficacy of medical devices:

As described later in Section "6.B Outline of the review conducted by PMDA," the clinical studies of the IVL System show a favorable outcome, demonstrating its efficacy and safety in patients with severely calcified, *de novo* coronary lesions. The IVL System conforms to Articles 3 and 6.

(3) PMDA's view on the conformity of the IVL System to Article 7, which specifies requirements for the chemical properties, biological safety, and other aspects of medical devices:

As described earlier in Section "2.(2) Physicochemical properties," Section "2.(4).B Outline of the review conducted by PMDA," and Section "2.(6).B Outline of the review conducted by PMDA," the chemical properties, and other aspects of the IVL System were justified. The IVL System conforms to Article 7.

(4) PMDA's view on the conformity of the IVL System to Article 8, which specifies the prevention of microbial contamination of medical devices:

As described later in Section "5.B. Outline of the review conducted by PMDA," prevention of microbial contamination of the IVL System was justified. The IVL System conforms to Article 8.

(5) PMDA's view on the conformity of the IVL System to Article 9, which specifies considerations regarding the environment in which the IVL System is used concomitantly with other medical devices:

As described later in Section "6.B Outline of the review conducted by PMDA," no adverse event related to the IVL System has been reported in patients with a pacemaker or implantable cardioverter defibrillator (ICD). In addition, users are appropriately warned of the possibility and risk of interactions between the IVL System and other medical devices through release of information including precautions or provision of the information to users via instructions for use, etc. ("Information on Precautions, etc."). The IVL System conforms to Article 9.

(6) PMDA's view on the conformity of the IVL System to Article 13, which specifies considerations for active medical devices, to Article 14, which specifies considerations for mechanical risks of medical devices, and to Article 15, which specifies considerations for medical devices supplying energy:

As described earlier in Section "2.(3).B Outline of the review conducted by PMDA" and Section "2.(6).B Outline of the review conducted by PMDA," the considerations for active medical devices, mechanical risks of medical devices, and medical devices supplying energy in using the IVL System were justified. The IVL System conforms to Articles 13, 14, and 15.

(7) PMDA's view on the conformity to Article 17, which specifies requirements for provision of information to users via the Information on Precautions, etc.:

As described later in Section "6.B Outline of the review conducted by PMDA," it is essential for users to understand the principles and risks of the IVL System, and to appropriately identify

eligible patients for treatment with the IVL System in order to maintain its risk-benefit balance. To this end, information should be provided through the Information on Precautions, etc., training, and other measures.

PMDA comprehensively reviewed the conformity of the IVL System to the Essential Principles and, concluded that there was no particular problem.

4. Risk Management

4.A Summary of the data submitted

The applicant submitted data summarizing the risk management system and the risk management activities implemented for the IVL System in accordance with ISO 14971 "Medical devices – Application of risk management to medical devices."

4.B Outline of the review conducted by PMDA

PMDA comprehensively reviewed the document on risk management, taking into account the discussion presented in Section "3.B Outline of the review conducted by PMDA," and concluded that there was no particular problem.

5. Manufacturing Process

5.A Summary of the data submitted

The applicant submitted data on the in-process tests during the manufacturing process of the IVL System and sterilization methods for the IVL Catheter (sterilization validation and bacterial endotoxin test).

5.B Outline of the review conducted by PMDA

PMDA reviewed the data on the manufacturing process, and concluded that there was no particular problem in the submitted data.

6. Clinical Data or Alternative Data Accepted by the Minister of Health, Labour and Welfare

6.A Summary of the data submitted

The applicant submitted the clinical evaluation data of the IVL System in the form of results from the Disrupt CAD III Study (pivotal study) conducted in the U.S. and Europe, and the Disrupt CAD IV Study (bridging study) conducted in Japan (Table 6).

Table 6. Clinical study data included in the present application

Study	Country (number of sites)	Follow-up period	Data submitted
Disrupt CAD III Study	US, the United Kingdom (UK), France, and Germany (47)	2 years	30-day results: Evaluation data 1-year results: Reference data
Disrupt CAD IV Study	Japan (8)	2 years	30-day results: Evaluation data 1-year results: Reference data

6.A.(1) Disrupt CAD III Study (study period, ongoing since January 2019)

The Disrupt CAD III Study was a prospective, multicenter, single-arm study to evaluate the safety and efficacy of the IVL System for the treatment of severely calcified, *de novo* coronary lesions prior to stenting. Table 7 shows a summary of the clinical study.

Table 7. Outline of the Disrupt CAD III Study

Item	Outline
Objectives	To evaluate the safety and efficacy of the IVL System for the treatment of severely calcified, *de novo* coronary lesions prior to stenting
Type of study	Prospective, multicenter, single-arm study
Study population	Subjects with calcified, *de novo* coronary lesions and stable, unstable, or asymptomatic ischemia eligible for percutaneous coronary intervention
Sample size	47 for Roll-in, 384 for pivotal
Primary endpoints	Primary safety endpoint Freedom from major adverse cardiac events (MACE) within 30 days of the index procedure. MACE was defined as the composite occurrence of the following events: • Cardiac death, or • Myocardial Infarction (MI): Defined as CK-MB >3 times the upper limit of institutional normal (ULN) with or without new pathologic Q wave at discharge (periprocedural MI), and using the Fourth Universal Definition of Myocardial Infarction beyond discharge (spontaneous MI), or • Target Vessel Revascularization (TVR): Defined as revascularization at the target vessel (including the target lesion) after the completion of the index procedure. All of potential MACEs were adjudicated by an independent Clinical Events Committee (CEC). Primary efficacy endpoint Procedural success, which is defined as stent delivery with a residual in-stent stenosis <50% (core laboratory assessed with angiography) and without in-hospital MACE.
Key inclusion criteria	• Patients aged ≥18 years • Patients with native coronary artery disease (including stable or unstable angina and silent ischemia) eligible for PCI • Left ventricular ejection fraction >25% within 6 months • Single *de novo* target lesion stenosis of protected left main coronary trunk or left anterior descending artery, right coronary artery or left circumflex artery with: a. stenosis of ≥70% and <100% or b. stenosis ≥50% and <70% (visually assessed) with evidence of ischemia via positive for stress test, or fractional flow reserve value ≤0.80, or instantaneous wave-free ratio <0.90 or IVUS or OCT minimum lumen area ≤4.0 mm² • The lesion length must not exceed 40 mm. • The target vessel must have thrombolysis in myocardial infarction (TIMI) flow 3 at baseline. • Evidence of calcification at the lesion site by, a) angiography, with fluoroscopic radio-opacities noted without cardiac motion prior to contrast injection involving both sides of the arterial wall in at least 1 location and total length of calcium of at least 15 mm and extending partially into the target lesion, or by b) IVUS or OCT, with presence of ≥270 degrees of calcium on at least 1 cross section
Key exclusion criteria	• Unable to tolerate dual antiplatelet therapy for at least 6 months. • Patients experienced an acute MI (ST elevation MI [STEMI] or non-ST evaluation MI [non-STEMI]) within 30 days prior to index procedure • New York Heart Association class III or IV heart failure • Patients with renal failure with serum creatinine >2.5 mg/dL or chronic dialysis • Uncontrolled diabetes mellitus defined as a hemoglobin A1c ≥10% • Patients in cardiogenic shock or with clinical evidence of left-sided heart failure (S3 gallop, pulmonary rales, oliguria, or hypoxemia) • Uncontrolled severe hypertension (systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg) • Unprotected left main diameter stenosis >30% • Target vessel is excessively tortuous (defined as the presence of 2 or more bends >90° or 3 or more bends >75°). • Definite or possible thrombus (by angiography or intravascular imaging) in the target vessel • Evidence of aneurysm in target vessel within 10 mm of the target lesion • Target lesion is an ostial location (left anterior descending artery, left circumflex artery, or right coronary artery, within 5 mm of ostium) or an unprotected left main lesion • Target lesion is a bifurcation with ostial diameter stenosis ≥30%. • The second lesion with >50% stenosis in the same target vessel as the target lesion including its side branches

The Disrupt CAD III Study was conducted to evaluate the efficacy and safety of the IVL System for the treatment of severely calcified, *de novo* coronary lesions prior to stenting. The study design was

similar to that of the ORBIT II Study, which was a pivotal study of the approved product "Diamondback 360 Coronary Orbital Atherectomy System." The performance goals for the primary endpoints of the study were calculated based on the results of the ORBIT II Study; and 84.4% for the primary safety endpoint and 83.4% for the primary efficacy endpoint were established. The overall sample size was determined based on the primary safety endpoint. Assuming the 30-day MACE-free rate of 89.6%, one-sided significance level of 5%, power of 90%, and dropout rate of 5%, the sample size was estimated to be 392 (minimum sample size required for evaluation, 372). Secondary endpoints included device crossing success, procedural success, and angiographic complications. Figure 3 shows the subject composition of the Disrupt CAD III Study. In this study, 98.2% (377 of 384) of pivotal subjects received treatment with the IVL System. Six subjects were investigational device delivery failures. One subject did not receive treatment with the IVL System because an error occurred in the IVL generator after the IVL Catheter crossed through the lesion.

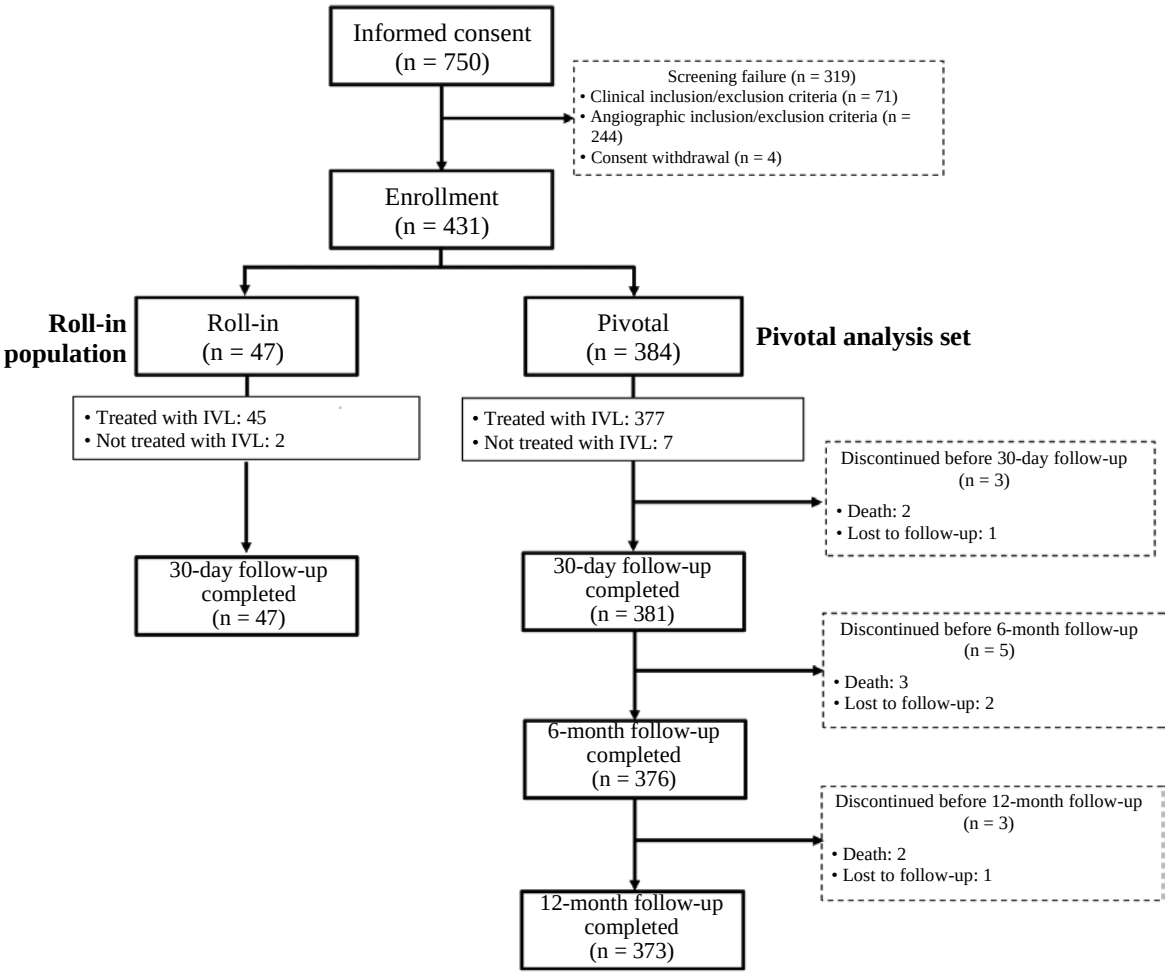

Figure 3. Subject composition of the Disrupt CAD III Study

6.A.(1).1) Patient demographics and baseline characteristics

Table 8 shows the demographics and baseline characteristics of pivotal subjects in this study and Table 9 shows pre-procedural angiographic characteristics.

Table 8. Patient characteristics

Item	Pivotal (N = 384)
Age (years), Median (minimum, maximum)	71.0 (43.0, 95.0)
Sex	
Male	76.6% (294/384)
Female	23.4% (90/384)
Race	
White	82.8% (318/384)
Black and African American	3.1% (12/384)
Asian	3.4% (13/384)
Native American or Alaska Native	0.5% (2/384)
Native Hawaiian or other Pacific Islander	0.3% (1/384)
Not specified	9.9% (38/384)
Ethnicity	
Hispanic or Latino	4.2% (16/384)
Non-Hispanic or Latino	85.9% (330/384)
Not specified	9.9% (38/384)
Diabetes mellitus	40.1% (154/384)
Hyperlipidemia	89.1% (342/384)
Hypertension	89.1% (342/384)
Prior stroke or transient cerebral ischemia attacks	7.6% (29/384)
Myocardial infarction	18.0% (69/384)
Prior coronary intervention	46.9% (180/384)
Prior CABG	9.4% (36/384)
Prior non-coronary interventional or surgical heart procedure	3.1% (12/384)
Peripheral vascular disease	13.0% (50/384)
Congestive cardiac failure	12.2% (47/384)
Arrhythmia	20.6% (79/384)
Pacemaker	4.7% (18/384)
ICD/CRT-D	1.6% (6/384)
Smoking	55.2% (212/384)
Renal insufficiency	12.0% (46/384)

Table 9. Pre-procedural angiographic characteristics (core laboratory assessed)

Item	Pivotal (N = 384)
Target lesion vessel, % (n/N)	
Left anterior descending artery	56.5% (217/384)
Right coronary artery	29.2% (112/384)
Left circumflex artery	12.8% (49/384)
Left main coronary trunk	1.6% (6/384)
Bypass graft	0.0% (0/384)
Lesion length (mm), mean ± SD	26.09 ± 11.68 (N = 381)
Reference vessel diameter (mm), mean ± SD	3.03 ± 0.47 (N = 381)
Minimum lumen diameter (mm), mean ± SD	1.06 ± 0.36 (N = 381)
Percent diameter stenosis (%), mean ± SD	65.1 ± 10.8 (N = 381)
Eccentric (%) (n/N)	3.1% (12/384)
Calcification (%) (n/N), severe*	100.0% (384/384)
Calcification length (mm), mean ± SD	47.85 ± 18.81 (N = 384)
Bifurcation/trifurcation (%) (n/N)	29.9% (115/384)
* Definition of "severe": Fluoroscopic radio-opacities noted without cardiac motion prior to contrast injection typically involving both sides of the arterial lumen	

6.A.(1).2) Study results

6.A.(1).2).(a) Treatment procedure using the IVL System

In this study, 98.2% (377 of 384) of subjects in the pivotal cohort received treatment with the IVL System, and 99.2% (381 of 384) of subjects underwent stenting. Pre-dilatation was required in 55.2% (212 of 384) of subjects to deliver the IVL Catheter to the target lesions. The mean number of the IVL Catheter per lesion was 1.2 ± 0.5. The mean number of pulses delivered was 68.8 ± 31.9 (minimum, 20.0; maximum, 160.0; median, 70.0). In the pivotal cohort, 20.7% (78 of 377) of subjects required post-dilatation immediately after treatment with the IVL System (post-IVL). Of them, 28 subjects

(35.9%) had post-IVL residual in-stent stenosis of ≥50% and underwent post-dilatation according to the protocol. The mean number of DESs per subject was 1.3 ± 0.5. Post-stent dilatation was required in 99.0% (377 of 381) of subjects. The total procedural time in the pivotal cohort was 59.0 ± 29.6 minutes. The total X-ray fluoroscopy time was 19.1 ± 12.4 minutes, with the total amount of contrast media being 167.9 ± 71.9 cc.

Table 10 shows post-IVL and post-stent angiographic characteristics in the pivotal cohort.

Table 10. Post-IVL and post-stent angiographic characteristics (core laboratory assessed)

Item	Pivotal (n = 384)	
	Post-IVL	Post-stent (in-stent)
Minimum lumen diameter (mm), mean ± SD	1.87 ± 0.48 (n = 341)	2.74 ± 0.43 (n = 381)
Percent diameter stenosis (%), mean ± SD	37.2 ± 13.5 (n = 341)	11.9 ± 7.1 (n = 341)
Acute gain diameter (mm), mean ± SD	0.82 ± 0.48 (n = 339)	1.68 ± 0.46 (n = 378)

6.A.(1).2).(b) Primary endpoints

The analysis of the primary safety endpoint included all pivotal subjects with or without MACE who completed 30-day (±7 days) follow-up visits (n = 383), excluding 1 subject who was lost to follow-up after discharge on Day 2. The observed 30-day MACE-free rate was 92.2% (353 of 383 subjects), with the lower bound of the one-sided 95% confidence interval of 89.9%, which was higher than the performance goal of 84.4%. These results rejected the null hypothesis, and the primary safety endpoint was met ($P < 0.0001$).

Table 11 shows the components of the composite primary safety endpoint. Most of the events (27 of 30 events, 90.0%) at 30 days occurred during the peri-operative period. The in-hospital MACE rate was 7.0%.

Table 11. Components of the primary safety endpoint (Pivotal analysis Set)

Cumulative MACE rates	In-hospital N = 384	30-day follow-up[1] N = 383
MACE[2,3]	7.0% (27/384)	7.8% (30/383)
Cardiac death	0.3% (1/384)	0.5% (2/383)
Non-Q-wave MI[4]	5.7% (22/384)	6.0% (23/383)
Q-wave MI	1.0% (4/384)	1.6% (6/383)
TVR	0.5% (2/384)	1.6% (6/383)

1. One subject was excluded from the primary safety endpoint analysis because of insufficient follow-up (<23 days).
2. All MACEs were adjudicated by an independent CEC.
3. Some subjects failed >1 component of the MACE criteria. Therefore, the categories are not mutually exclusive.
4. Myocardial infarction (MI) is defined as creatine kinase MB (CK-MB) >3 times the upper limit of institutional normal (ULN) with or without new pathologic Q wave at discharge (periprocedural MI), and using the Fourth Universal Definition of Myocardial Infarction beyond discharge (spontaneous MI).

The primary efficacy analysis included all pivotal subjects (N = 384). The observed procedural success rate was 92.4% (355 of 384 subjects), with the lower bound of the one-sided 95% confidence interval of 90.2%, which was higher than the performance goal of 83.4%. These results rejected the null hypothesis, and the primary efficacy endpoint was met ($P < 0.0001$).

Table 12 shows the components of the composite primary efficacy endpoint.

Table 12. Components of the primary efficacy endpoint (Pivotal analysis set)

Primary efficacy endpoint: Procedural success	% (n/N)
Procedural success[1,2]	92.4% (355/384)
Stent delivered[3]	99.2% (381/384)
<50% residual in-stent stenosis	100.0% (381/381)
Without in-hospital MACE	93.0% (357/384)

1. Procedural success defined as stent delivery with a residual in-stent stenosis <50% (core laboratory assessed) and without in-hospital MACE (CEC adjudicated)
2. Some subjects failed >1 component of the procedural success criteria. Therefore, the categories are not mutually exclusive.
3. Three subjects did not receive a stent; 2 subjects were IVL device delivery failures that did not receive any therapy on the day of the index procedure; and 1 subject had failed stent delivery after successful IVL.

6.A.(1).2).(c) Adverse events, etc.

Table 13 shows a summary of site-reported device- or procedure-related serious adverse events observed through 30 days. Death occurred in 2 subjects during the 30-day follow-up period and the events were confirmed as cardiac death. One of them was a 69-year-old man, who had slow flow and Type B dissection proximal to the left anterior descending artery after treatment with the IVL System. Despite insertion of a DES, abrupt closure occurred. The subject received an intra-aortic balloon pump (IABP) and vasopressor therapy, which did not prevent ventricular fibrillation from occurring. He had cardiac arrest and underwent emergency coronary artery bypass graft (CABG). After the surgery, he experienced respiratory failure and cardiogenic shock, and was switched to palliative care because of his aggravated clinical condition. The IABP was removed. The subject died 9 days after the procedure. The cardiac death was adjudicated by the Clinical Events Committee (CEC) as being probably device-related and definitely procedure-related. The other was a 90-year-old woman, who was treated with the IVL System at a lesion proximal to the left anterior descending artery, received a DES, and then was discharged from the site with a stable condition. The subject had ST-elevation myocardial infarction (STEMI) at 6 days post-procedure, which was thought to be stent thrombosis. The subject was transferred to the catheterization laboratory. Thrombotic occlusion was observed distal to the left anterior descending artery. The subject received medical treatment and an IABP and was followed up, but eventually died. The cardiac death was adjudicated by the CEC as being possibly device-related and definitely procedure-related.

Table 13. Summary of site-reported serious adverse events observed through 30 days (Pivotal analysis set)

	Device-related		Procedure-related	
System Organ Class/Preferred Term	Subject % (n/N)	Event N	Subject % (n/N)	Event N
Total subjects with serious adverse events	2.1% (8/384)	8	6.8% (26/384)	38
Blood and lymphatic system disorders	0.0% (0/384)	0	0.3% (1/384)	1
Haemorrhagic anaemia	0.0% (0/384)	0	0.3% (1/384)	1
Cardiac disorders	1.8% (7/384)	7	5.5% (21/384)	25
Coronary artery dissection	0.8% (3/384)	3	2.9% (11/384)	11
Myocardial infarction	0.3% (1/384)	1	1.8% (7/384)	7
Arrhythmia	0.0% (0/384)	0	0.5% (2/384)	2
Angina pectoris	0.3% (1/384)	1	0.5% (2/384)	2
Coronary artery perforation	0.3% (1/384)	1	0.3% (1/384)	1
Coronary artery thrombosis	0.0% (0/384)	0	0.3% (1/384)	1
Myocardial ischaemia	0.3% (1/384)	1	0.3% (1/384)	1
Congenital, familial and genetic disorders	0.0% (0/384)	0	0.3% (1/384)	1
Congenital coronary artery malformation	0.0% (0/384)	0	0.3% (1/384)	1
Hepatobiliary disorders	0.0% (0/384)	0	0.3% (1/384)	1
Hepatic failure	0.0% (0/384)	0	0.3% (1/384)	1
Injury, poisoning and procedural complications	0.0% (0/384)	0	0.3% (1/384)	1
Vascular access site haematoma	0.0% (0/384)	0	0.3% (1/384)	1
Investigations	0.0% (0/384)	0	0.5% (2/384)	2
Myocardial necrosis marker increased (elevated cardiac biomarker)	0.0% (0/384)	0	0.5% (2/384)	2
Nervous system disorders	0.0% (0/384)	0	0.3% (1/384)	1
Cerebrovascular disorder	0.0% (0/384)	0	0.3% (1/384)	1
Renal and urinary disorders	0.0% (0/384)	0	0.3% (1/384)	1
Renal failure	0.0% (0/384)	0	0.3% (1/384)	1
Respiratory, thoracic and mediastinal disorders	0.0% (0/384)	0	0.3% (1/384)	1
Respiratory failure	0.0% (0/384)	0	0.3% (1/384)	1
Vascular disorders	0.3% (1/384)	1	1.0% (4/384)	4
Hypotension	0.3% (1/384)	1	0.5% (2/384)	2
Shock	0.0% (0/384)	0	0.3% (1/384)	1
Peripheral ischaemia	0.0% (0/384)	0	0.3% (1/384)	1

Note: A subject experiencing multiple occurrences of an adverse event was counted once per system organ class and preferred term.

Table 14 shows angiographic complications observed during a series of procedures with the IVL System.

Table 14. Angiographic complications (core laboratory assessed) (Pivotal analysis set)

	Pre-IVL (N = 384)	Post-IVL (N = 384)	After final pre-dilatation before stent (N = 384)	Post-stent (N = 384)	Post OCT-IVUS (N = 384)	Final[1] (N = 384)	All time points (N = 384)
Serious angiographic complication[2]	0.0% (0/384)	2.6% (9/341)	1.6% (1/64)	0.8% (3/357)	0.0% (0/122)	0.5% (2/384)	3.1% (12/384)
Any dissection	0.0% (0/384)	17.6% (60/341)	6.3% (4/64)	2.2% (8/357)	0.0% (0/122)	2.3% (9/384)	18.0% (69/384)
Dissection[3]							
A	0.0% (0/384)	0.3% (1/341)	0.0% (0/64)	0.0% (0/357)	0.0% (0/122)	0.3% (1/384)	0.5% (2/384)
B	0.0% (0/384)	10.6% (36/341)	3.1% (2/64)	2.2% (8/357)	0.0% (0/122)	1.6% (6/384)	12.2% (47/384)
C	0.0% (0/384)	4.7% (16/341)	1.6% (1/64)	0.0% (0/357)	0.0% (0/122)	0.3% (1/384)	4.4% (17/384)
Serious dissection (D-F)							
D	0.0% (0/384)	1.5% (5/341)	0.0% (0/64)	0.0% (0/357)	0.0% (0/122)	0.0% (0/384)	1.3% (5/384)
E	0.0% (0/384)	0.6% (2/341)	0.0% (0/64)	0.0% (0/357)	0.0% (0/122)	0.0% (0/384)	0.5% (2/384)
F	0.0% (0/384)	0.0% (0/341)	1.6% (1/64)	0.0% (0/357)	0.0% (0/122)	0.3% (1/384)	0.3% (1/384)
Perforation[4]							
Any	0.0% (0/384)	0.0% (0/341)	0.0% (0/64)	0.6% (2/357)	0.0% (0/122)	0.3% (1/384)	0.5% (2/384)
I	0.0% (0/384)	0.0% (0/341)	0.0% (0/64)	0.0% (0/357)	0.0% (0/122)	0.0% (0/384)	0.0% (0/384)
II	0.0% (0/384)	0.0% (0/341)	0.0% (0/64)	0.3% (1/357)	0.0% (0/122)	0.3% (1/384)	0.3% (1/384)
III	0.0% (0/384)	0.0% (0/341)	0.0% (0/64)	0.3% (1/357)	0.0% (0/122)	0.0% (0/384)	0.3% (1/384)
Abrupt closure	0.0% (0/384)	0.0% (0/341)	1.6% (1/64)	0.0% (0/357)	0.0% (0/122)	0.3% (1/384)	0.3% (1/384)
Slow flow	0.0% (0/384)	0.6% (2/341)	0.0% (0/64)	0.3% (1/357)	0.0% (0/122)	0.0% (0/384)	0.8% (3/384)
No reflow	0.0% (0/384)	0.0% (0/341)	0.0% (0/64)	0.0% (0/357)	0.0% (0/122)	0.0% (0/384)	0.0% (0/384)

1. The final image is the one chosen by the analyst based on optimal projection, image quality, etc. from the post-procedural images obtained after all devices have been removed and the procedure has been completed.
2. Serious angiographic complications include severe dissection (Type D-F), perforation, abrupt closure, slow flow, and no reflow.
3. Dissections were categorized per the NHLBI classification system.
4. Perforations were categorized per the Ellis classification for coronary perforation

6.A.(1).2).(d) Results through 12 months

Table 15 shows the results through 12 months in the Disrupt CAD III Study.

Table 15. Major adverse cardiac events (MACE) rates through 12 months in the Disrupt CAD III Study

	In-hospital	30 days[1]	6 months	12 months
MACE[2,3]	7.0% (27/384)	7.8% (30/383)	10.2% (39)	13.8% (52)
Cardiac death	0.3% (1/384)	0.5% (2/383)	0.8% (3)	1.1% (4)
Non-Q-wave MI[4]	5.7% (22/384)	6.0% (23/383)	7.8% (30)	9.2% (35)
Q-wave MI	1.0% (4/384)	1.6% (6/383)	1.6% (6)	1.6% (6)
TVR	0.5% (2/384)	1.6% (6/383)	2.9% (11)	6.0% (22)

Note: In-hospital and 30-day MACE rates were presented as binomial proportions, with the number of events to the number of evaluable subjects. 6- and 12-month MACE rates were presented as Kaplan-Meier estimates event rates, with the number of events.

1. One subject was excluded from the primary safety endpoint analysis (30-day MACE analysis) because of insufficient follow-up (<23 days).
2. All MACEs were adjudicated by an independent CEC.
3. Some subjects failed ≥2 components of the MACE criteria. Therefore, the categories are not mutually exclusive.
4. Myocardial infarction (MI) is defined as CK-MB >3 times the ULN with or without new pathologic Q wave at discharge (periprocedural MI), and using the Fourth Universal Definition of Myocardial Infarction beyond discharge (spontaneous MI).

6.A.(2) Disrupt CAD IV Study (Japanese study) (study period, ongoing since November 2019)

Japanese subjects were enrolled in the Disrupt CAD IV Study using similar eligibility criteria to those of the Disrupt CAD III Study. The primary safety and efficacy endpoints of the Disrupt CAD IV Study were compared with those in a similar population consisting of propensity score- matched subjects from the Disrupt CAD III Study. The ratio of the subject population of the Disrupt CAD IV Study to that of the Disrupt CAD III Study was 1:5. The non-inferiority of the outcome in the Disrupt CAD IV cohort to that in the matched Disrupt CAD III cohort was assessed for the primary safety and efficacy endpoints. A total of 72 subjects (8 roll-in subjects and 64 intent-to-treat [ITT] subjects) were enrolled in the Disrupt CAD IV Study.

Figure 4 shows the subject composition of the Disrupt CAD IV Study.

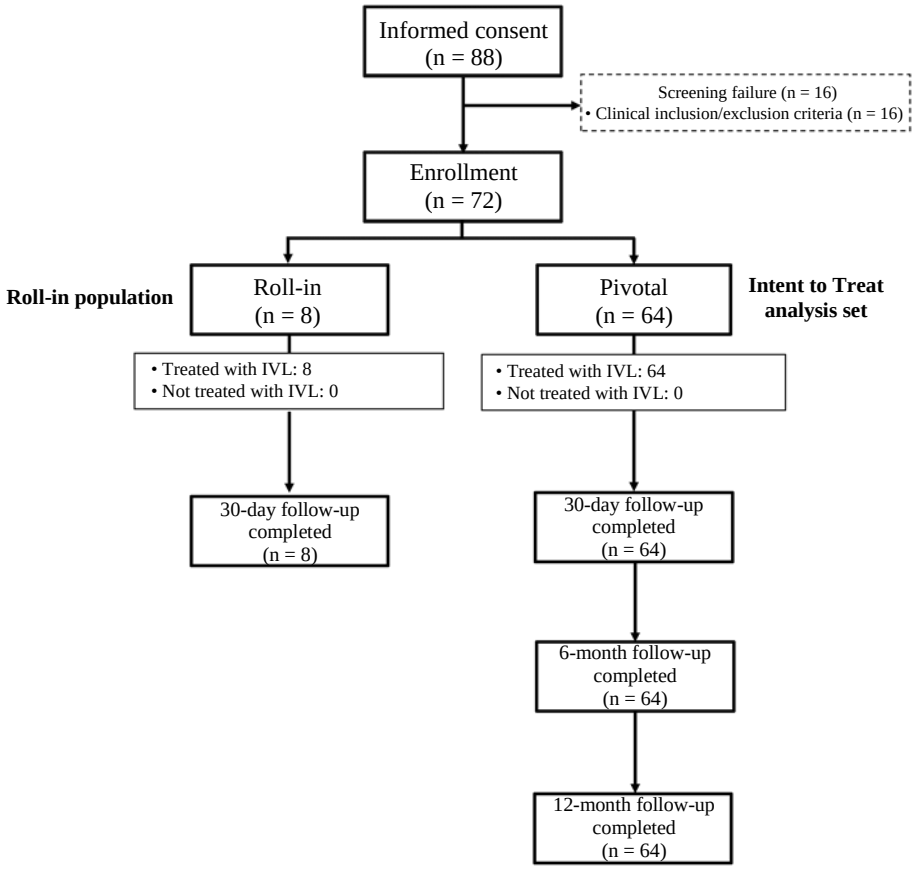

Figure 4. Subject composition of the Disrupt CAD IV Study

6.A.(2).1) Patient demographics and baseline characteristics

Table 16 shows the demographics and baseline characteristics of ITT subjects in this study. Table 17 shows pre-procedural angiographic characteristics.

Table 16. Patient demographics and baseline characteristics

Item	Intent to Treat (N = 64)
Age (years), Median (minimum, maximum)	74.5 (60.0, 92.0)
Sex	
Male	75.0% (48/64)
Female	25.0% (16/64)
Diabetes mellitus	48.4% (31/64)
Hyperlipidemia	85.9% (55/64)
Hypertension	82.8% (53/64)
Prior stroke or transient cerebral ischemia attacks	20.3% (13/64)
Myocardial infarction	20.3% (13/64)
Prior coronary intervention	46.9% (30/64)
Prior CABG	3.1% (2/64)
Prior coronary intervention or cardiac surgery	9.4% (6/64)
Peripheral vascular disease	17.2% (11/64)
Congestive cardiac failure	9.4% (6/64)
Arrhythmia	12.5% (8/64)
Pacemaker	1.6% (1/64)
ICD/CRT-D	0.0% (0/64)
Smoking	62.5% (40/64)
Renal insufficiency	1.6% (1/64)

Table 17. Pre-procedural angiographic characteristics (core laboratory assessed)

Item	Intent to Treat (N = 64)
Target lesion vessel, % (n/N)	
Left anterior descending artery	75.0% (48/64)
Right coronary artery	17.2% (11/64)
Left circumflex artery	6.3% (4/64)
Left main coronary trunk	1.6% (1/64)
Bypass graft	0.0% (0/64)
Lesion length (mm), mean ± SD	27.48 ± 10.36 (N = 63)
Reference vessel diameter (mm), mean ± SD	2.91 ± 0.36 (N = 64)
Minimum lumen diameter (mm), mean ± SD	1.00 ± 0.34 (N = 64)
Percent diameter stenosis (%), mean ± SD	65.8 ± 10.9 (N = 64)
Eccentric (%) (n/N)	1.6% (1/64)
Calcification (%) (n/N), severe*	100.0% (64/64)
Calcification length (mm), mean ± SD	49.79 ± 15.54 (N = 64)
Bifurcation/trifurcation (%) (n/N)	34.4% (22/64)
* Definition of "severe": Fluoroscopic radio-opacities noted without cardiac motion prior to contrast injection typically involving both sides of the arterial lumen	

6.A.(2).2) Study results

6.A.(2).2).(a) Treatment procedure with the IVL System

All of the 64 subjects in the ITT cohort received treatment with the IVL System and underwent stenting. Pre-dilatation was required in 20.3% (13 of 64) of subjects to deliver the IVL Catheter to the target lesions. The mean number of the IVL Catheter per lesion was 1.6 ± 0.7. The mean number of pulses delivered was 104.4 ± 55.7 (minimum, 20.0; maximum, 240.0; median, 80.0). The mean number of DESs per subject was 1.1 ± 0.3. All of the subjects required post-stent dilatation. The total procedural time in the ITT cohort was 62.5 ± 23.1 minutes. The total X-ray fluoroscopy time was 22.2 ± 11.1 minutes, with the total amount of contrast media being 173.5 ± 56.5 cc.

Table 18 shows post-IVL and post-stent angiographic characteristics in the ITT cohort.

Table 18. Post-IVL and post-stent angiographic characteristics (core laboratory assessed)

Item	Intent to Treat (n = 64)	
	Post-IVL	Post-stent (in-stent)
Minimum lumen diameter (mm), mean ± SD	1.82 ± 0.49 (n = 55)	2.67 ± 0.36 (n = 64)
Percent diameter stenosis (%), mean ± SD	38.0 ± 12.9 (n = 55)	9.9 ± 5.7 (n = 64)
Acute gain diameter (mm), mean ± SD	0.82 ± 0.48 (n = 55)	1.67 ± 0.37 (n = 64)

6.A.(2).2).(b) Primary endpoints

The ITT population (n = 64) of the Disrupt CAD IV Study was used as the primary analysis set for evaluation of the primary endpoint. The ITT population was compared with the matched Disrupt CAD III cohort (n = 320).

All of the ITT subjects in the Disrupt CAD IV Study were followed up through 30 days for primary safety evaluation. This population was used for analysis of the primary safety endpoint (n = 64). One subject in the matched Disrupt CAD III cohort was excluded from the primary safety analysis because of insufficient follow-up (<23 days).

Table 19 shows the results of non-inferiority analysis of the primary safety endpoint. The 30-day MACE-free rate was 93.8% (60 of 64 subjects) in the Disrupt CAD IV Study and 91.2% (291 of 319 subjects) in the matched Disrupt CAD III cohort (observational difference, 2.53%). The lower bound

of the one-sided 90% confidence interval for the difference was −3.79%, which was higher than the non-inferiority margin of −9.36%. These results rejected the null hypothesis, and the primary safety endpoint was met (P = 0.0080).

Table 19. Non-inferiority analysis of the primary safety endpoint (ITT population)

Primary safety endpoint	Disrupt CAD IV Study (n = 64)	Disrupt CAD III Study[1] (n = 320)	Difference (lower bound of 90% confidence interval)[2]	*P*-value[2]	Conclusion[3]
30-day MACE-free rate	93.8% (60/64)	91.2% (291/319)	2.53% [-3.79%]	0.0080	Non-inferiority demonstrated.
MACE	6.3% (4/64)	8.8% (28/319)[4]			
Cardiac death	0.0% (0/64)	0.6% (2/319)			
Non-Q-wave MI	6.3% (4/64)	6.9% (22/319)			
Q-wave MI	0.0% (0/64)	1.6% (5/319)			
TVR	0.0% (0/64)	1.9% (6/319)			

1. Subjects in the Disrupt CAD III Study were matched at the ratio of 5:1 using propensity score based on the following parameters: age, sex, diabetes mellitus (on medical treatment), prior coronary artery bypass surgery, estimated glomerular filtration rate (calculated using Modification of Diet in Renal Disease formula), reference vessel diameter, lesion length, and lesion at bifurcated site. One subject in the Disrupt CAD III Study was excluded from the analysis of the primary safety endpoint because of insufficient follow-up (<23 days). This subject was lost to follow-up at Day 2, without any MACE.
2. The one-sided *P*-value for the difference and the lower bound of the confidence interval were calculated using Farrington-Manning non-inferiority test of 2 binomial proportions assuming the non-inferiority margin of 9.36% and one-sided significance level of 0.10.
3. Non-inferiority is demonstrated when the lower bound of 90% confidence interval is higher than −9.36%.
4. Some subjects in the Disrupt CAD III Study met ≥2 components of the MACE criteria. Therefore, the categories are not mutually exclusive.

Table 20 shows the cumulative MACE and component rates during hospitalization and through 30 days in the Disrupt CAD IV Study. All events (100%, 4 of 4 subjects) observed at 30 days in the ITT population of the Disrupt CAD IV Study were in-hospital non-Q-wave MI. The non-Q-wave MI event was associated with an increased biomarker, which met the protocol-specified definition of MI.

Table 20. Primary safety endpoint components (ITT population)

Cumulative MACE rates	In-hospital n = 64	30-day follow-up n = 64
MACE[1]	6.3% (4/64)	6.3% (4/64)
Cardiac death	0.0% (0/64)	0.0% (0/64)
Non-Q-wave MI[2]	6.3% (4/64)	6.3% (4/64)
Q-wave MI	0.0% (0/64)	0.0% (0/64)
TVR	0.0% (0/64)	0.0% (0/64)

1. All MACEs were adjudicated by an independent CEC.
2. Myocardial infarction (MI) is defined as CK-MB >3 times the ULN with or without new pathologic Q wave at discharge (periprocedural MI), and using the Fourth Universal Definition of Myocardial Infarction beyond discharge (spontaneous MI).

The primary efficacy analysis included all subjects (64 in the Disrupt CAD IV Study, 320 in the matched Disrupt CAD III cohort).

Table 21 shows the results of non-inferiority analysis of the primary efficacy endpoint. The procedural success rate was 93.8% (60 of 64 subjects) in the Disrupt CAD IV Study and 91.6% (293 of 320 subjects) in the matched Disrupt CAD III cohort (observational difference, 2.19%). The lower bound of one-sided 90% confidence interval for the observational difference was −4.16%, which was higher than the non-inferiority margin of −10.0%. These results rejected the null hypothesis, and the primary efficacy endpoint was met (P = 0.0070).

Table 21. Non-inferiority analysis of the primary efficacy endpoint (ITT population)

Primary efficacy endpoint	Disrupt CAD IV Study (n = 64)	Disrupt CAD III Study[2] (n = 320)	Difference (lower bound of 90% confidence interval)[3]	*P*-value[3]	Conclusion[4]
Procedural success[1]	93.8% (60/64)	91.6% (293/320)	2.19% [-4.16%]	0.0070	Non-inferiority demonstrated.
Stent delivered	100.0% (64/64)	99.1% (317/320)			
<50% residual in-stent stenosis	100.0% (64/64)	100.0% (317/317)[5]			
Without in-hospital MACE	93.8% (60/64)	92.2% (295/320)			

1. Procedural success defined as stent delivery with a residual in-stent stenosis <50% (core laboratory assessed) and without in-hospital MACE (CEC adjudicated)
2. Some subjects in the Disrupt CAD III Study met ≥2 components of the procedural success criteria. Therefore, the categories are not mutually exclusive.
3. Subjects in the Disrupt CAD III Study were matched at the ratio of 5:1 using propensity scores. The propensity score model included the following parameters: age, sex, diabetes mellitus (on medical treatment), prior coronary artery bypass surgery, estimated glomerular filtration rate (calculated using Modification of Diet in Renal Disease formula), reference vessel diameter, lesion length, and lesion at bifurcated site. The one-sided *P*-value for the difference and the lower bound of the confidence interval were calculated using Farrington-Manning non-inferiority test of 2 binomial proportions assuming the non-inferiority margin of 10.0% and one-sided significance level of 0.10.
4. Non-inferiority is demonstrated when the lower bound of 90% confidence interval is higher than −10.0%.
5. Three subjects in the Disrupt CAD III Study did not meet the primary efficacy endpoint because of stent failure.

6.A.(2).2).(c) Adverse events, etc.

Table 22 shows a summary of site-reported device- or procedure-related serious adverse events observed through 30 days.

Table 22. Summary of site-reported serious adverse events observed through 30 days (ITT population)

	Device-related		Procedure-related	
System Organ Class/Preferred Term	Subject % (n/N)	Event N	Subject % (n/N)	Event N
Number of subjects with serious adverse events	1.6% (1/64)	2	1.6% (1/64)	2
Cardiac disorders	1.6% (1/64)	2	1.6% (1/64)	2
Coronary artery occlusion	1.6% (1/64)	1	1.6% (1/64)	1
Myocardial infarction	1.6% (1/64)	1	1.6% (1/64)	1

Note: A subject experiencing multiple occurrences of an adverse event was counted once per system organ class and preferred term.

Table 23 shows angiographic complications observed during a series of procedures with the IVL System. In the Disrupt CAD IV Study, vascular perforation, abrupt closure, slow flow, or no reflow did not occur at any time point.

Table 23. Angiographic complications (core laboratory assessed) (ITT population)

	Pre-IVL (N = 64)	Post-IVL (N = 64)	After final pre-dilatation before stent (N = 64)	Post-stent (N = 64)	Post OCT-IVUS (N = 64)	Final[1] (N = 64)	All time points (N = 64)
Serious angiographic complication[2]	0.0% (0/64)	1.7% (1/58)	0.0% (0/2)	0.0% (0/64)	0.0% (0/54)	0.0% (0/64)	1.6% (1/64)
Any dissection	0.0% (0/64)	25.9% (15/58)	0.0% (0/2)	1.6% (1/64)	1.9% (1/54)	3.1% (2/64)	23.4% (15/64)
Dissection[3]							
A	0.0% (0/64)	0.0% (0/58)	0.0% (0/2)	0.0% (0/64)	0.0% (0/54)	0.0% (0/64)	0.0% (0/64)
B	0.0% (0/64)	19.0% (11/58)	0.0% (0/2)	1.6% (1/64)	1.9% (1/54)	3.1% (2/64)	17.2% (11/64)
C	0.0% (0/64)	5.2% (3/58)	0.0% (0/2)	0.0% (0/64)	0.0% (0/54)	0.0% (0/64)	4.7% (3/64)
Serious dissection (D-F)							
D	0.0% (0/64)	1.7% (1/58)	0.0% (0/2)	0.0% (0/64)	0.0% (0/54)	0.0% (0/64)	1.6% (1/64)
E	0.0% (0/64)	0.0% (0/58)	0.0% (0/2)	0.0% (0/64)	0.0% (0/54)	0.0% (0/64)	0.0% (0/64)
F	0.0% (0/64)	0.0% (0/58)	0.0% (0/2)	0.0% (0/64)	0.0% (0/54)	0.0% (0/64)	0.0% (0/64)

1. The final image is the one chosen by the analyst based on optimal projection, image quality, etc. from the post-procedural images obtained after all devices have been removed and the procedure has been completed.
2. Serious angiographic complications include severe dissection (Type D-F), perforation, abrupt closure, slow flow, and no reflow.
3. Dissections were categorized per the NHLBI classification system.

6.A.(2).2).(d) Results through 12 months

Table 24 shows the results through 12 months in the Disrupt CAD IV Study.

Table 24. MACE rate through 12 months in the Disrupt CAD IV Study

	In-hospital	30 days	6 months	12 months
MACE	6.3% (4/64)	6.3% (4/64)	7.8% (5)	9.4% (6)
Cardiac death	0.0% (0/64)	0.0% (0/64)	0.0% (0)	0.0% (0)
Non-Q-wave MI	6.3% (4/64)	6.3% (4/64)	6.3% (4)	6.3% (4)
Q-wave MI	0.0% (0/64)	0.0% (0/64)	0.0% (0)	0.0% (0)
TVR	0.0% (0/64)	0.0% (0/64)	3.1% (2)	4.7% (3)

Note: In-hospital and 30-day MACE rates were presented as binomial proportions, with the number of events to the number of evaluable subjects. 6- and 12-months MACE rates were presented as Kaplan-Meier estimates event rates, with the number of events.

6.B Outline of the review conducted by PMDA

6.B.(1) Efficacy and safety of the IVL System demonstrated by the clinical study results submitted

6.B.(1).1) Study design

PMDA reviewed the justification of the study design as shown below.

6.B.(1).1).(a) Use of the results from the foreign clinical study as evaluation data

PMDA's view:

While the medical environment for percutaneous coronary interventions does not appear to substantially differ between Japan and other countries, the prevalence rate of severe coronary artery calcification may not be similar between Japan and overseas. The foreign Disrupt CAD III Study and the Japanese Disrupt CAD IV Study used the same definition for severe calcification, which is a reasonable definition considering the severity of calcification in Japan. Subjects with severe calcification were enrolled in both the Disrupt CAD III and Disrupt CAD IV Studies. It is reasonable to use the results of the foreign Disrupt CAD III Study as pivotal evaluation data.

6.B.(1).1).(b) Endpoints, performance goals, etc.

PMDA's view:

The IVL System is a medical device designed to assist stenting by pretreating calcified coronary artery lesions as is the case of the approved product "Diamondback 360 Coronary Orbital Atherectomy System." Considering the above, the efficacy and safety endpoints as well as performance goals used in the Disrupt CAD III Study, which was conducted using the similar study design to that of the ORBIT II Study, were acceptable. Taking into account that the Japanese Disrupt CAD IV Study was intended to extrapolate data from the foreign Disrupt CAD III Study to the Japanese population, the study design of the Disrupt CAD IV Study using the same endpoints, eligibility criteria, etc. as those of the Disrupt CAD III Study is appropriate.

6.B.(1).2) Efficacy

The procedural success rate in the Disrupt CAD III Study was 92.4% (355 of 384 subjects), with the lower bound of the one-sided 95% confidence interval of 90.2%, which was higher than the performance goal of 83.4%. The procedural success rate in the Disrupt CAD IV Study was 93.8% (60 of 64 subjects), showing the non-inferiority to the matched Disrupt CAD III cohort (91.6%, 293 of 320 subjects).

PMDA asked the applicant to explain whether the efficacy of the IVL System may differ depending on the morphology of a calcified lesion (e.g., whether it is eccentric, concentric, or nodular).

The applicant's explanation:

The morphology of calcified lesions was analyzed using pooled data from the OCT sub-studies of Disrupt CAD I to IV Studies (n = 262). These analyses were performed by an independent OCT core laboratory.

The mean maximum calcium angle and thickness of the whole lesion were 270° ± 81° and 0.96 ± 0.25 mm, respectively. OCT imaging revealed calcium fractures in 68% of the lesions analyzed. The minimum stent area was 6.2 ± 1.9 mm^2. The stent expansion at the maximum calcium site was 103% ± 29%. The depth of fracture was 0.5 ± 0.2 mm. Fractures affecting all layers of calcium were observed in 72% of lesions disrupted. These findings indicate the effect of treatment with the IVL System on deep calcification.[4]

Table 25 shows the results of analysis[5] on eccentric and concentric calcification. Table 26 shows the results of analysis[6] on calcification with and without calcified nodules. As shown in these tables, the results show the consistent efficacy of the IVL System, regardless of the morphology of calcification. [redacted]. All resolved after stenting and the incidence of serious angiographic complications was 0% at the end of the procedure. On the basis of these findings, the applicant determined that there was no particular safety problem.

Table 25. Analysis on eccentric and concentric calcification

	Eccentric	Concentric			*P*-value*
	≤180°	181°-270°	271°-359°	360°	
n	56	57	51	66	
Minimum stent area (mm^2)	6.1 ± 2.1	6.0 ± 1.9	6.1 ± 1.8	6.2 ± 1.9	0.94
Percent stent expansion at the maximum calcium site (%)	104 ± 30	101 ± 29	98 ± 27	105 ± 27	0.65
* The *P*-values of the minimum stent area and percent stent expansion indicate cross comparisons of all 4 groups.					

Table 26. Analysis on calcification with and without calcified nodule

	With calcified nodule	Without calcified nodule	*P*-value
n	54	194	
Minimum stent area (mm^2)	6.3 ± 2.1	6.0 ± 1.9	0.41
Percent stent expansion at the maximum calcium site (%)	101 ± 28	104 ± 30	0.87

PMDA's view:

Treatment with the IVL System was associated with a high procedural success rate in the patient population having severe calcification, in which treatment has been challenging. Stent expansion was favorable, regardless of the eccentricity of calcified lesions. In addition, no complication specific to certain lesion morphology has been reported to date. Taken together with the comments from the Expert Discussion, PMDA concluded that the use of the IVL System is effective for the treatment of severely calcified, *de novo* coronary lesions prior to stenting.

6.B.(1).3) Safety

6.B.(1).3).(a) Results of the clinical studies

The 30-day MACE-free rate in the Disrupt CAD III Study was 92.2% (353 of 383 subjects), with the lower bound of the one-sided 95% confidence interval of 89.9%, which was higher than the performance goal of 84.4%. The 30-day MACE-free rate in the Disrupt CAD IV Study was 93.8% (60 of 64 subjects), showing the non-inferiority to the matched Disrupt CAD III cohort (91.2%, 291 of 319 subjects).

PMDA's view:

The safety results are clinically acceptable as they met the predefined performance goal. Nevertheless, it should be confirmed that treatment with the IVL System will not affect the long-term outcomes. PMDA asked the applicant to discuss the long-term results of treatment with the IVL System, in light of the results with the approved medical devices.

The applicant's explanation:

The ORBIT II Study of the approved product "Diamondback 360 Coronary Orbital Atherectomy System" revealed the MACE rate of 16.9%, cardiac death rate of 3.2%, myocardial infarction rate of 10.6%, and target vessel revascularization (TVR) rate of 5.8% at 12 months.[7] The COAST Study of the approved medical device showed the MACE rate of 22.2%, cardiac death rate of 1.0%, myocardial infarction rate of 14.0%, and TVR rate of 9.4% at 12 months.[8] The ROTAXUS Study of the "Rotablator" showed the MACE rate of 24.2%, myocardial infarction rate of 6.7%, and TVR rate of 16.7% at 9 months.[9]

Taken together with the long-term results with these approved medical devices, the study findings indicate no particular safety problems of the IVL System. Most of the cases of myocardial infarction at 30 days in the Disrupt CAD III Study were not related to the target blood vessels (10 of 12 events, 83.3%). All of the 10 events were adjudicated to be unrelated to the investigational device or procedure by the CEC.

PMDA's view:
Although a direct comparison between the long-term results of the IVL System and the clinical study results of the approved medical devices cannot be made, the results with the IVL System were comparable to available data. Based on the 1-year results, treatment with the IVL System was unlikely to be associated with a particular risk.

6.B.(1).3).(b) Risks specific to the IVL System

PMDA asked the applicant to explain in detail the following risks, based on the characteristics of the IVL System.

i) Effects of acoustic pressure pulses on hemodynamics

The applicant's explanation:
In the Disrupt CAD III Study, a hemodynamic sub-study was conducted to assess the effects (ventricular capture, arrhythmia, and hypotension) of the IVL System on the hemodynamics during the index procedure.

Of 416 subjects with evaluable hemodynamic data in the Disrupt CAD III Study, 171 subjects (41.1%) had ventricular capture during the index procedure because of the use of the IVL System. In the group of subjects with ventricular capture, the incidence of an investigator-assessed decrease in systolic blood pressure during the IVL procedure was higher than that in the group of subjects without ventricular capture (40.5%, 66 of 163 subjects vs. 24.5%, 58 of 237 subjects; $P = 0.0007$). However, the magnitude of a decrease in blood pressure did not differ between the 2 groups. A transient decrease in blood pressure that was assessed as clinically significant by the investigator was observed only in limited subjects. There was no difference in the incidence of a clinically significant decrease in blood pressure between the 2 groups (1.5%, 1 of 66 subjects in the ventricular capture group vs. 3.4%, 2 of 58 subjects in the non-ventricular capture group; $P = 0.5988$). Subjects with ventricular capture induced by the IVL System had no persistent ventricular arrhythmia.

Ventricular capture induced by the IVL System ("IVL-induced ventricular capture") is a known risk. Normal rhythm and blood pressure were restored in the subjects with IVL-induced ventricular capture rapidly once the use of the IVL System was completed. No serious adverse events, such as arrhythmia, were reported. The risk of IVL-induced ventricular capture can be clinically acceptable provided that the following precautionary information is included in the Information on Precautions, etc.: The electrocardiogram (ECG) rhythm and arterial pressure of the patient should be monitored during the procedure with the IVL System, and the use of the IVL System should be suspended temporarily if any clinical problem occurs.

PMDA's view:
The hemodynamic effects associated with IVL-induced ventricular capture include a decrease in blood pressure. This was, however, a transient event associated with the use of the IVL System and did not lead to a clinically significant adverse event, such as arrhythmia. Taken together, the applicant's response that the information on this risk would be included in the Information on Precautions, etc. is acceptable.

ii) Effects of acoustic pressure pulses on pacemaker/ICD

The applicant's explanation:
A pooled analysis of the safety data from the Disrupt CAD I to IV Studies was performed to assess a relationship between adverse events related to pacemaker/ICD and the IVL System. The pooled safety analysis set (683 subjects in total) included 42 subjects (6.1%) with a pacemaker/ICD. There were neither pacemaker/ICD-related events (e.g., inappropriate shock and transient pacing disturbance) nor hemodynamic adverse events (e.g., hypotension, shock, and unstable hemodynamics). Of the subjects with a pacemaker/ICD, 3 subjects (7.1%) experienced arrhythmia ≥30 days after the index procedure. None of the cases was related to the IVL System or index procedure. These 3 subjects were enrolled in the Disrupt CAD III Study. All of them had a medical history of arrhythmia.

On the basis of the above data and the fact that the IVL System generates acoustic pressure pulses of very low energy (<8 μJ), the use of the IVL System appears to be safe in patients with a pacemaker/ICD. The risk of pacemaker/ICD-related adverse events can be clinically acceptable provided that the following precautionary information is included in the Information on Precautions, etc.: (1) IVL-induced capture on ECG may interact with device sensing function in patients with a pacemaker/ICD; and (2) the ECG rhythm and arterial pressure of the patient should be monitored during the procedure with the IVL System (as with hemodynamics described above), and the use of the IVL System should be suspended temporarily if any clinical problem occurs.

PMDA's view:
According to the applicant's explanation, the currently available data show no risk of the interaction between the IVL System and pacemaker/ICD. The applicant's response that the information on this risk would be included in the Information on Precautions, etc. is acceptable.

iii) Balloon rupture/loss of pressure

The applicant's explanation:
A total of 527 catheters were used in 431 subjects (the total of roll-in and pivotal subjects) in the Disrupt CAD III Study. During the study, a modification was made to the original IVL Catheter to slightly increase the balloon double wall thickness, with expectation of improving the structural stability of the balloon and reducing the risk for loss of pressure during treatment. As a result, 342 catheters with the original design and 185 catheters with the modified design (the IVL Catheter) were used. The incidence of balloon rupture/loss of pressure was 9.4% (32 of 342 catheters) with the original design versus 5.9% (11 of 185 catheters) with the modified design, showing a decrease in the incidence of balloon rupture/loss of pressure. Table 27 shows the results of an analysis that evaluated the association between balloon loss of pressure and post-IVL angiographic complications or 30-day

MACE. The results show no significant difference in the incidence of 30-day MACE or post-IVL angiographic complications between subjects with and without balloon loss of pressure. A multivariate analysis indicated the length of calcification as a significant independent predictor of post-IVL dissections and balloon rupture/loss of pressure. Calcification appears to be a root cause of the tendency for a higher incidence of dissection in the loss of pressure group.

Table 27. 30-day MACE and post-IVL angiographic complications in subjects with and without balloon loss of pressure

	Loss of pressure	No loss of pressure	*P*-value
30-day MACE[1]	7.7% (3/39)	8.2% (32/391)	1.0000
Post-IVL angiographic complications (core laboratory assessed)[2]			
Dissection	29.7% (11/37)	16.2% (56/345)	0.0650
Perforation	0.0% (0/37)	0.0% (0/345)	1.0000
Abrupt closure	0.0% (0/37)	0.0% (0/345)	1.0000
Slow flow	2.7% (1/37)	0.3% (1/345)	0.1846
No reflow	0.0% (0/37)	0.0% (0/345)	1.0000

1. A total of 430 subjects (roll-in + pivotal) were evaluated for 30-day MACE; 1 subject was excluded from the analysis because of insufficient follow-up.
2. A total of 382 subjects had post-IVL images available for analysis.

The incidence of balloon rupture/loss of pressure in the Japanese Disrupt CAD IV Study, where only the modified catheter was used, was 5.2% (6 of 115 catheters) in roll-in and ITT subjects. The risk of these events is similar to that of balloon rupture in conventional balloon angioplasty commonly referred to in literature on coronary artery calcification,[10,11,12] and it is clinically acceptable.

PMDA's view:
The reduced risk of balloon rupture/loss of pressure is clinically acceptable, because (i) the IVL System is used in severely calcified lesions; (ii) the incidence of balloon rupture/loss of pressure with the IVL System does not substantially differ from that reported in balloon angioplasty of calcified lesions; and (iii) there is no association between balloon loss of pressure and angiographic complications or 30-day MACE in the subjects who were treated with the IVL System.

6.B.(2) Clinical positioning of the IVL System

6.B.(2).1) Post-IVL intervention treatment

The applicant's explanation:
The clinical studies demonstrated the efficacy and safety of the IVL System for the treatment of severely calcified, *de novo* coronary lesions prior to stenting. The approved intended use of the IVL System overseas specifies that it be used prior to stenting. Recently, DESs are commonly used in PCI around the world. Drug-coated balloons (DCBs) are also used in PCI considering the balance between the benefit of the treatment and the risk of adverse reactions associated with the use of dual antiplatelets. The intended use of balloon catheters and atherectomy devices approved for the treatment of calcified coronary arteries in Japan specifies no post-procedural treatment. DCBs can be chosen after pretreatment of calcified lesions with these devices. Given this, post-IVL interventions other than stenting should be allowed.

PMDA asked the applicant to explain the efficacy and safety of post-IVL treatment options other than stenting.

The applicant's explanation:

The efficacy and safety of post-IVL treatment options other than stenting can be supported mainly by the following 2 analyses:

- The publications on the treatment with DCBs with and without atherectomy in patients with calcified coronary arteries in Japan[13,14,15,16,17] reported no serious angiographic complication with poor prognosis, suggesting the usefulness of DCB in patients ineligible for DES placement. In the pooled data analysis involving 628 subjects (72 sites in 12 countries) from the Disrupt CAD I to IV Studies,[18] post-IVL angiographic evaluation was conducted (n = 561). The analysis showed an increased minimum lumen diameter and a decreased percent diameter stenosis after the treatment with the IVL System. For complications, no episode of post-IVL perforation, abrupt closure, or no reflow was reported. The incidence of dissections with blood flow restriction (Grade D or higher) was as low as 1.8%, also the incidence of slow flow was as low as 0.4%. The incidence of serious angiographic complications after atherectomy in the ORBIT II Study of the approved product "Diamondback 360 Coronary Orbital Atherectomy System" was 2.3% for severe dissection (Grade C or higher), 0.9% for perforation, 0.2% for slow flow, 0% for no reflow, and 0.9% for abrupt closure.[2] These results are unlikely to suggest that post-IVL stentless treatment is associated with the exacerbation of the disease condition, compared with the conventional procedures.

- Literature search on post-IVL treatments other than stenting found 15 publications (7 observational registries and 8 case reports) regarding the combination of the IVL System and DCB between 2019 and 2021. These publications included a report on the use of the IVL System in patients with in-stent restenosis. Four of them reported the use of DCBs in new lesions, for which the use of the IVL System is indicated, after treatment with the IVL System.[19,20,21,22] None of the publications reported angiographic complications, including DCB-related thrombotic events. A follow-up for up to 15 months confirmed the clinical stability of the patients.[20]

PMDA's view:

Currently, DESs are the first-line option for PCI in Japan.[23] As explained by the applicant, stenting is the standard therapy. However, a stentless technique using a percutaneous old balloon angioplasty (POBA) or DCB without a stent is also accepted for treatment of lesions in small blood vessels or bifurcated sites. The incidence of post-IVL serious angiographic complications was low. Abrupt closure can be a risk for stentless treatment. This risk can, however, be controlled by observing the blood vessel for a severe dissection by IVUS, etc. as with the conventional procedures. Two cases of perforation in the Disrupt CAD III Study occurred after stenting. Taken together with the comments from the Expert Discussion, treating physicians should be allowed to select a post-IVL treatment option and the use of the IVL System should not be limited to the use prior to stenting.

6.B.(2).2) Intended use

PMDA's view:

In light of the above discussions, the intended use of the IVL System in Japan, unlike overseas, should not be limited to the use prior to stenting. The clinical studies submitted were conducted in patients with severely calcified lesions and therefore did not confirm the clinical usefulness of the IVL System in the treatment of non-severe calcification. Taken together with the comments from the Expert

Discussion, the IVL System should be indicated for the treatment of severely calcified lesions. Based on the above review, the appropriate intended use of the IVL System is as shown below.

Intended Use of the IVL Catheter

C^2 Coronary IVL Catheter is intended to be used to disrupt severely calcified, *de novo* coronary lesions allowing subsequent dilatation of a coronary artery stenosis.

Intended Use of the IVL Generator

IVL Generator is intended to be used to disrupt severely calcified, *de novo* coronary lesions.

6.B.(3) Post-marketing safety measures

6.B.(3).1) Qualification for users and medical institutions, and training, etc.

PMDA asked the applicant to explain safety measures, including requirements for users and medical institutions, and training.

The applicant's explanation:

The IVL System must be used by physicians experienced in PCI since it uses the same platform as that of percutaneous transluminal coronary angioplasty (PTCA) balloon catheters. No special facilities are required for treatment with the IVL System. The safety of this technique will be assured if the IVL System is used at medical institutions equipped with a system that provides appropriate emergency surgical support or emergency surgery as is the case of the standard PCI. The same requirements are implemented in Europe and the US.

In both the Disrupt CAD III and Disrupt CAD IV Studies, the first subject enrolled at each site was regarded as a roll-in subject. The treating physicians at sites had the first experience with the IVL System in their roll-in subjects. As shown in Table 28, the results did not differ between the roll-in and pivotal cohorts. This suggests that the learning curve is almost flat. In addition, the IVL procedure does not involve cutting of a calcified lesion unlike the approved atherectomy devices, and the incidence of angiographic complications such as coronary artery dissections and perforation was low. Given these facts, there will be no safety problem provided that this procedure is performed by physicians experienced in coronary artery intervention at medical institutions equipped with the above system after adequate training.

Table 28. Results in roll-in subjects of the Disrupt CAD III and Disrupt CAD IV Studies

	Disrupt CAD III Study		Disrupt CAD IV Study	
	Roll-in	Pivotal	Roll-in	ITT
n	47	384	8	64
Procedural success	87.2%	92.4%	100%	93.8%
Device crossing success	93.6%	95.8%	100%	98.4%
30-day MACE-free rate	89.4%	92.2%	100%	93.8%
Total procedure time (minute)	65.1 ± 26.1	59.0 ± 29.6	72.8 ± 32.6	62.5 ± 23.1

Since the IVL System and the approved medical devices use different principles, physicians need to appropriately understand the differences in their characteristics and to be trained for the proper safe use of the IVL System prior to its clinical use. The applicant will discuss and provide training programs in cooperation with the Japanese Association of Cardiovascular Intervention and Therapeutic

(CVIT). For product introduction, the applicant and the CVIT are planning to co-host a joint training session for the potential users of the IVL System. To ensure the safety, the IVL System will be introduced into the clinical setting on a step-by-step basis, according to a plan. The training program will include the following:

- Description of the IVL System
- The principle of the IVL System and its differences from that of the approved medical devices
- Clinical data
- Patient selection (e.g., explanation by presenting the Information on Precautions, etc., points to consider for proper safe use, and specific cases)
- Troubleshooting

PMDA's view:
Taken together with the comments from the Expert Discussion, there was no particular problem with the applicant's explanation about the requirements for users and medical institutions or plans on post-marketing training in cooperation with a related academic society and stepwise product introduction.

6.B.(3).2) Use-results survey

The applicant's explanation:
No use-results survey is required in Japan for the following reasons:

- The pooled data analysis involving 628 subjects (72 sites in 12 countries) from the Disrupt CAD I to IV Studies conducted overseas and in Japan[18] showed the 30-day MACE free-rate of 92.7% and the procedure success rate of 92.4%. The incidence of serious angiographic complications was 2.1% after the use of the IVL System and 0.3% at the final angiography. No episode of IVL-related perforation, abrupt closure, or no reflow was reported, suggesting no particular problem with the use of the IVL System. These analysis results support the safety of the IVL System for the treatment of severe calcification.
- Out of Japan, [redacted] catheters and [redacted] generators have been sold to date, with no report of unexpected adverse events and a low incidence of adverse events.
- The Japanese Disrupt CAD IV Study showed favorable results, including 1-year results.

PMDA's view:
The IVL System, which uses the same platform as that of common PTCA balloon catheters, does not involve a novel procedure, but it uses a new principle to disrupt calcification. In view of this fact, the applicant's explanations, the characteristics of the principle, and the non-clinical and clinical results, the IVL System is unlikely to impose a new risk, not reported with the conventional procedures, even when the aforementioned medical devices other than stents are used after the treatment with the IVL System. Taken together with the comments from the Expert Discussion, the following conclusion is reached: With safety measures including the standard post-marketing malfunction reporting, the risk for the treatment with the IVL System can be controlled as is the case of the conventional procedures. No use-results survey is required to ensure the efficacy and safety of the IVL System in the post-marketing setting in Japan, provided that physicians take sufficient post-marketing training.

7. Plan for Post-marketing Surveillance etc. Stipulated in Paragraph 1 of Article 2 of Ministerial Ordinance on Good Post-marketing Study Practice for Medical Devices

7.A Summary of the data submitted

The applicant did not plan to conduct any post-marketing surveillance and therefore submitted no post-marketing surveillance plan.

7.B Outline of the review conducted by PMDA

The applicant decided not to conduct post-marketing surveillance as discussed in Section 6 above, and PMDA concluded that the applicant's decision was acceptable.

8. Documents Relating to Information on Precautions, etc. Specified in Paragraph 1 of Article 63-2 of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices, in Relation to Notification Pursuant to the Same Paragraph of the Act

8.A Summary of the data submitted

The applicant submitted Information on Precautions, etc. (draft) as an attachment in accordance with the Notification titled "Application for Marketing Approval of Medical Devices" (PFSB Notification No. 1120-5, dated November 20, 2014).

8.B Outline of the review conducted by PMDA

On the basis of the comments raised in the Expert Discussion, as described earlier in Section "6.B Outline of the review conducted by PMDA," PMDA has concluded that there are no particular problems with the proposed Information on Precautions, etc., provided that the applicant provides necessary precautions.

III. Results of Compliance Assessment Concerning the New Medical Device Application Data and Conclusion Reached by PMDA

PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The medical device application data were subjected to a document-based inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

IV. Overall Evaluation

The review of the applications for the IVL System focused on (1) the efficacy and safety of the IVL System and (2) post-marketing safety measures. Taking account of comments raised in the Expert Discussion, PMDA reached the conclusions shown below.

(1) Efficacy and safety of the IVL System

The Disrupt CAD III Study was conducted to evaluate the efficacy and safety of the IVL System for the treatment of severely calcified, *de novo* coronary lesions prior to stenting. The primary safety endpoint was the "30-day MACE-free rate" and the primary efficacy endpoint was the "rate of procedural success defined as stent delivery with a residual in-stent stenosis <50% (core laboratory assessed) and without in-hospital MACE." Both endpoints met the pre-specified performance goal. The Disrupt CAD IV Study, a Japanese clinical study, demonstrated that the results of the Disrupt CAD III Study could be extrapolated to the Japanese population.

Currently, DESs are the first-line option for PCI in Japan. However, a stentless technique using a POBA or DCB without a stent is also accepted for the treatment of lesions in small blood vessels or bifurcated sites. The submitted clinical study results, which addressed stent therapy, showed a low incidence of post-IVL angiographic complications, indicating that the risk for stentless therapy can be controlled as is the case of the conventional procedures. Treating physicians should be allowed to select a post-IVL treatment option and the use of the IVL System should not be limited to the use prior to stenting.

(2) Post-marketing safety measures

The foreign Disrupt CAD III Study and the Japanese Disrupt CAD IV Study showed favorable results, including 1-year results. In addition, no particular problem with treatment with the IVL System has been reported overseas. The IVL System is unlikely to impose a new risk, not reported with the conventional procedures, even when medical devices other than stents are used after treatment with the IVL System. Its risk can be controlled as is the case of the conventional procedures. In summary, the efficacy and safety of the IVL System can be ensured by providing precautionary advice based on the differences in the principle between the IVL System and the approved medical devices and by providing sufficient post-marketing training. No use-results survey is required.

As a result of the above review, PMDA has concluded that the IVL System may be approved after modifying the intended use as shown below.

Intended Use of the IVL Catheter

C^2 Coronary IVL Catheter is intended to be used to disrupt severely calcified, *de novo* coronary lesions allowing subsequent dilatation of a coronary artery stenosis.

Intended Use of the IVL Generator

IVL Generator is intended to be used to disrupt severely calcified, *de novo* coronary lesions.

The product is not classified as a biological product or a specified biological product. The product is not designated as a medical device subject to a use-results survey.

PMDA has concluded that the present application should be subjected to deliberation by the Committee on Medical Devices and *In-vitro* Diagnostics.

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